THE EFFECT OF FENTANYL VS KETAMINE ON THE INCIDENCE 0F EMERGENCE DELIRIUM FROM SEVOFLURANE ANESTHESIA IN PEDIATRIC PATIENTS UNDERGOING TONSILLECTOMY

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF UNIVERSITY

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BRANCH X – ANAESTHESIOLOGY

THE TAMIL NADU

Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

MAY, 2018

CERTIFICATE

This is to certify that this dissertation " **THE EFFECT OF FENTANYL VS KETAMINE ON THE INCIDENCE 0F EMERGENCE DELIRIUM FROM SEVOFLURANE ANESTHESIA IN PEDIATRIC PATIENTS UNDERGOING TONSILLECTOMY** " presented here in by Dr. G.SHANMUGA PRIYA is an original work done in the Department of Anaesthesiology, Kanyakumari Govt Medical College Hospital, Asaripallam, Nagercoil for the award of Degree of M.D (Branch – X) Anaesthesiology under my direct supervision and guidance, during the academic period of 2016 – 2018

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DECLARATION

I, Dr. G.SHANMUGA PRIYA hereby declare that the dissertation titled "**THE EFFECT OF FENTANYL VS KETAMINE ON THE INCIDENCE 0F EMERGENCE DELIRIUM FROM SEVOFLURANE ANESTHESIA IN PEDIATRIC PATIENTS UNDERGOING TONSILLECTOMY**" has been done by me. This is submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.D. degree, Branch – X (ANAESTHESIOLOGY) Degree Examination to be held in April 2017.

Place : Asaripallam

Date : Dr. G.SHANMUGA PRIYA

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Dated: .11.2016

CERTIFICATE OF ETHICAL COMMITTEE APPROVAL

The Institutional Ethical Committee meeting was conducted on 10.11.2016 at 11.00 am at Medical Education Unit, Kanyakumari Govt. Medical College Asaripallam, to give approval of your study title "The effect of fentanyl Vs Ketamine on the incidence of emergence agitation after sevoflurance anesthesia in pediatric patients undergoing tonsillectomy."

The following members of the Ethical Committee attended the Meeting.

1. Chairman : Dr. M. Kannan. M.D.,
   Prof of Anaesthesia (Retired)

2. Basic Medical Scientists : 1.Dr. R. Rajesh M.D.,
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4.	Representative of Non Government Voluntary Agency	:	Mrs. Jesintha Dharma
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6.	Statistician	:	Dr. J. Merlin Premala Ph.D
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8.	Member Secretary	:	Dr. T. Ashok Kumar M.D., Prof & HOD of Pharmacology Kanyakumari Govt. Medical College Asaripallam

The committee has given approval of your study subject to the following conditions

- The Study should be conducted in its presented form.
- The Progress of the study and any changes in the study to be informed to the committee
- Copy of the final result of study may be furnished to the committee.

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Urkund Analysis Result

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INTRODUCTION

Several studies have revealed that sevoflurane anesthesia even though having the advantage of rapid emergence and recovery has been associated with emergence delirium in pediatric age group. Several drugs has been investigated to reduce the occurrence and the severity of emergence delirium with variable outcome. These include propofol, fentanyl, ketamine, α 2 agonists like clonidine, dexmeditomidine and they are found to be effective in decreasing the incidence of emergence delirium .

Emergence delirium is a transient confusional state that is associated with emergence from general anesthesia. Emergence excitement is common in children, with an incidence of more than 30%. It usually occurs within the first 10 minutes of recovery but can have later onset in children who are brought to the recovery room asleep. Peak age of incidence is less than 5 yrs[24].

Child with emergence delirium appears wild and incoherent. They are inconsolable and does not appear to recognize familiar people [29].It usually lasts for 5- 15 minutes, self limiting, resolves quickly and is followed by an uneventful recovery. Even though it is usually self-limited; emergence delirium is still considered as worrisome side effect because of the risks of falling, self-injury to the child or to the surgical site, the stress caused to both

caregivers and families and increase in need for continuous monitoring of patients by recovery room staffs and physical restraint of patient.[3]

In children, emergence excitement is most frequently associated with rapid “wake up” from inhalational anesthesia. Although it has also been reported after isoflurane and, to a lesser extent, halothane anesthesia, emergence excitement is most often associated with the less-soluble vapors, sevoflurane and desflurane. There is 33% higher incidence of excitement during emergence (~21% versus ~15%) with sevoflurane anesthesia when compared to halothane. Incidence of emergence excitement is more a reflection of the anesthetic agent used rather than the rapidity of emergence.[24]

ETIOLOGICAL FACTORS

PREOPERATIVE RISK FACTORS

GENETICS:

Genetic polymorphism in the regions of IL-1,IL-6,IL-10,TNFα play an important role in the immune response and inflammatory pathway that may predispose the patient to post operative delirium[13]. Currently there are insufficient studies to explain the basis behind the genetic predisposition of emergence delirium

AGE:

Patients with age less than 40 years and age more than 64 years are more prone for emergence delirium[10]. Similarly pediatric patients with less than 5 years of age reported to have higher incidence of emergence delirium[24]. There are decreased levels of acetyl choline, dopamine, norepinephrine and GABA are present in both geriatric and pediatric population. Any disturbances to these neurotransmitters are implicated in development of emergence delirium[22].

BENZODIAZEPINES:

Studies have reported that preoperative use of benzodiazepines increase the risk of emergence delirium.[22]

Other drugs that are associated with emergence delirium [33]are

- Atropine
- Scopolamine
- Ketamine
- Barbiturates

PERIOPERATIVE RISK FACTORS

INHALATIONAL ANESTHETICS

Several studies have shown that there is direct correlation between the use of inhalational anesthetics and the occurrence of emergence delirium.[20]

Among the inhalational anesthetics emergence delirium appear more commonly with the use of sevoflurane than with desflurane and halothane.[2] This may be attributed to the low blood solubility which is a characteristic feature of newer inhalational anesthetics that cause rapid awakening thereby increasing the susceptibility of occurrence of emergence delirium.[11]

SURGERY:

The occurrence of emergence delirium is associated with the type of surgery that the patient undergoes [22].Patients who underwent breast and abdominal surgeries have higher incidence of emergence delirium [22]. Surgeries involving tonsils ,middle ear and eye are also shown to have increased incidence of emergence delirium. [20]

PAIN:

The level of pain is an independent contributing factor for the occurrence emergence delirium [22]. Several studies have shown that alleviation of pain has decreased the incidence of emergence delirium.[10,11]

Preoperative anxiety and underlying temperament of the patient undergoing surgery are also risk factors for occurrence of emergence delirium[24].

TEMPERAMENT:

Children who are more emotional, more impulsive, less social, and less adaptable to environmental changes were found to be at risk for development of emergence agitation. It may be due to the fact that there is some substrate innate to each child that may elicit a fearful response to outside stimuli, depending on the interaction between the child and the environment [33]. This reaction, which describes the "excitability, responsivity, or arousability" of the child, might be the underlying substrate from which both preoperative anxiety and emergence delirium arise .[18]

PREVENTION AND TREATMENT

Simple preventive measures should be taken to treat children at risk.

These include

- reducing preoperative anxiety,
- treating postoperative pain, and
- providing a stress-free environment for recovery.

Several medications had been investigated to prevent and treat emergence agitation and delirium

BENZODIAZEPINES:

Despite the increased risk of emergence delirium with preoperative use of benzodiazepines, studies have shown that there is decreased incidence of emergence delirium when the benzodiazepines is administered perioperatively.[21,25]

NSAIDs AND OPIODS:

Pain is an independent risk factor for emergence delirium especially in pediatric population. So adequate pain relief decreases the incidence of emergence delirium. Several studies have shown that NSAIDs like ketorolac[20] and opiods like fentanyl and remifentanyl [7,8,15] decreases the incidence of emergence delirium.

α 2 AGONISTS:

Among the α 2 agonists two drugs, clonidine and dexmeditomidine are shown to be effective in the management of emergence delirium

CLONIDINE:

Clonidine exhibit decrease in incidence of emergence delirium with an added advantage of good sedation during induction and better postoperative analgesia.[11]

DEXMEDITOMIDINE:

Dexmeditomidine has relatively benign safety profile and improved efficacy, hence it is preferred for prevention and management of emergence delirium. It also has an advantage of improved symptomatic coverage by decreasing the incidence of PONV, post operative pain, chill and restlessness associated with general anesthesia .[17]

KETAMINE:

Earlier studies have shown that ketamine itself is a risk factor for emergence delirium. However recent studies have shown that ketamine when given orally or intravenously in low doses is effective in preventing the occurrence of emergence delirium.[12,21,23]

When emergence delirium does occur, non-pharmacological treatment involves ensuring patient safety, excluding physical discomfort and reassuring the patient, parents and healthcare workers regarding its transient nature. Pharmacological 'rescue' treatments that have been reported to be effective include intravenous boluses of sedative agents such as midazolam 0.025 mg/kg[6] or propofol 0.5–1 mg/kg[16] and opioids such as intravenous fentanyl 1–2 µg/kg[34].

AIM OF THE STUDY

To compare the efficacy of Fentanyl 1μ/kg and Ketamine 0.5 mg/kg administered 10 minutes before the end of surgery for the development of emergence delirium and recovery profile in pediatric patients undergoing tonsillectomy

INHALATIONAL INDUCTION IN CHILDREN

Pediatric anesthesia is a subspecialty that has evolved because the needs of infants and young children are basically different from those of adults. The anesthesiologist should be aware of the child's cardiovascular, respiratory, renal, neuromuscular, and central nervous system responses to various drugs, as well as to physical and chemical stimuli, such as changes in blood oxygen and carbon dioxide tensions, pH, and body temperature. Their responses are different both qualitatively and quantitatively from those of adults and among different pediatric age groups. The pediatric anesthesiologist should always consider the child's emotional needs and create an environment that minimizes or abolishes fear and distress.[29]

The induction of anesthesia is the most crucial and stressful period of general anesthesia for the young patient as well as for the anesthesiologist. The consequences of this stressful experience by a child become apparent in the immediate post anesthetic period and may persist for weeks or even longer.

PSYCHOLOGICAL FACTORS

Stress and anxiety manifested in children before and during anesthetic induction result from the interaction between the child's personal predisposition such as age, maturity, personality, and past experiences in the hospital environment and the environmental factors like unfamiliar environment,

exposure to many strangers, the noise level, intensity of lights in the operating room. During the preoperative examination, it is extremely important to identify the child who is likely to develop extreme fear and anxiety before the induction of anesthesia .Premedication with sedatives has been shown to be most effective.[29]

The most intense fear of an infant or a young child is due to separation from the parents, often conceived as loss of love or abandonment. The sequence of reaction often observed is as follows: angry protest with panicky anxiety, depression and despair, and eventually apathy and detachment. Older children may be more concerned with painful procedures and the loss of self-control implicit with general anesthesia. Repeated hospitalizations for anesthesia and surgery may be associated with psychosocial disturbances in later childhood. In children old enough to experience fear and apprehension during anesthesia and surgery, the emotional factor may be of greater concern than the physical condition; it may represent the greatest problem of the perioperative course.

MEDICAL FACTORS

Upper respiratory tract infection (URI) is the most common problem the anesthesiologist has to deal with before the induction of anesthesia. Although a recent history or the presence of URI may not increase the risk of

long-term outcome beyond the immediate postoperative period, URI or lower respiratory tract infection and inflammation does increase the irritability and secretion of the respiratory tract and may increase the incidence of laryngospasm, bronchospasm, and perioperative hypoxemia.[29]

Risk factors for respiratory complications include endotracheal intubation, history of prematurity (even in older children), reactive airway disease , passive smoking, nasal congestion ,copious secretions, and airway surgery. Increased airway reactivity with viral respiratory infection lasts as long as 6 to 8 weeks. Prophylactic bronchodilator treatment should be given, before the induction of anesthesia and/or before the emergence from anesthesia and extubation.

If a child has had symptoms of URI with episodes of wheezing requiring bronchodilator treatment in the previous weeks, elective surgery should be postponed for at least 4 to 6 weeks after an episode of symptomatic asthma. The history of the child's steroid requirement over the past several months is important for determining if they should be given stress-dose steroid coverage.[29]

PREOPERATIVE FASTING

The purpose of preoperative fasting is to allow sufficient time for gastric emptying of ingested food and liquid so as to minimize the risk of aspiration of gastric contents into the lungs during anesthesia.

Children can be allowed to take clear fluids 2 hours prior to surgery. Infants less than 6 months of age on breast milk require 4 hours of fasting. Older infants over 6 months of age on milk or infant formula should be fasted for 6 hours; milk or infant formula should be considered as solid food because the fat is the main determinant delaying gastric emptying . Children on solid food, including toast, cereal, and juice with pulp, such as orange juice, are usually fasted for 8 hours or NPO after midnight prior to induction of anesthesia.[29]

PREMEDICATION

The use of premedication is most effective for reducing preoperative anxiety for young patients

HYPNOTICS:

The most common drug used for premedication is midazolam, a water-soluble benzodiazepine, in fruit-flavored syrup to mask its bitter taste given as 0.3 to 0.5 mg/kg orally. It is effective within 10 to 15 minutes.

Midazolam has also been used less frequently via the nasal route (0.2 to 0.3 mg/kg) or rectal route (0.3 mg/kg). In 10 to 15 minutes of oral medication administration, most children become calm, euphoric, or drowsy and are unsteady walking, and they must be held carefully or placed in bed. There is minimal separation anxiety when taken away from parents to the operating room.[29]

OPIOIDS

Opioid premedication is not frequently used in children because of potential respiratory depression. Oral transmucosal fentanyl citrate (OTFC) has the advantage of self-titration and has a relatively rapid onset without increases in gastric pH. However, it causes more preoperative and postoperative side effects such as pruritus, vomiting, and hypoxemia.[29]

KETAMINE

Intramuscular injection of ketamine in a relatively low dose (2 to 3 mg/kg,) is effective in uncooperative, combatant children as the last resort to avoid inhalation induction by force or for the insertion of an intravenous catheter. Ketamine may be combined with glycopyrrolate to reduce secretions. Ketamine has also been given via the oral, nasal transmucosal, or rectal routes. Ketamine solution (6 mg/kg) diluted with fruit-flavored syrup and given orally produced effective sedation in 12 minutes. Ketamine mixed with midazolam

was reported to produce a better anxiolysis than either drug alone. Nasal transmucosal ketamine also produce effective sedation.

CLONIDINE

Clonidine is an α_2-adrenergic receptor agonist shown to produce perioperative sedation and reduce the anesthetic requirement and postoperative analgesia. Oral clonidine (4 mcg/kg) provides good anxiolysis and sedation. A major limitation of oral clonidine as a premedicant, especially in day care surgery is that it must be given at least 60 minutes prior to induction.

PREANESTHETIC PREPARATION [29]

OPERATING ROOM PREPARATION :

Warm operating room

Turn on warming devices (e.g., warming blanket, intravenous line warmer, radiant light heat source)

ANESTHESIA EQUIPMENT :

Anesthesia machine checkout

Monitoring equipment (pulse oximeter, capnograph, anesthetic gas monitor) Precordial stethoscope with double-stick adhesive

Proper-size blood pressure cuff, pulse oximeter probe, temperature probe

Proper-size facemask

Oral and nasal airways

Tongue depressor

Laryngeal mask airway (LMA) if planned

Laryngoscope handle and at least two blades

Three sizes of endotracheal tubes

Stylet

Suction turned on with Yankauer suction tip or suction catheter

Adhesive tape torn and ready for use

Intravenous fluid bag connected to appropriate tubings and injection ports

Intravenous catheters

DRUGS :

Intravenous drugs drawn up

- Propofol and/or thiopental
- Atropine, succinylcholine, nondepolarizing muscle relaxant
- Reversal drugs (neostigmine, edrophonium, glycopyrrolate)
- Opioids (morphine, fentanyl, or remifentanil on infusion pump

INDUCTION

There are various techniques used for inducing general anesthesia in children. The induction techniques vary from inhalational, intravenous, and intramuscular, to rectal administration of anesthetics. Inhalational and intravenous methods are widely used nowadays.[29]

INHALATIONAL INDUCTION

Inhalation induction by mask is the most commonly used technique in pediatric anesthesia because it can be achieved easily and rapidly and is less objectionable than the insertion of an intravenous catheter.

If a child has dozed off while awaiting induction or is well sedated with premedication, anesthesia can be induced by the “steal technique,” with the child on the stretcher as originally described by Guedel in 1921. This can be achieved by blowing a high flow of 70% nitrous oxide in oxygen into the anesthesia mask while it is held closely over the face, without touching the skin

at first, and then placed gently on the face for a few minutes while increasing the concentration of sevoflurane up to 2 MAC before the child is moved to the operating table

The procedure should be smooth and continuous. The two most important monitoring equipment during an inhalation induction are a precordial stethoscope and a pulse oximeter. The stethoscope should be positioned over the left sternal border at the second to fourth intercostal space (not below the nipple line) with a double stick adhesive so that both the breath and heart sounds will be heard clearly.[29]

The first sign of anesthetic induction usually is the appearance of nystagmus; then the eyes usually close, respiration becomes slower, regular, and deeper, then shallower and more rapid, and the child becomes still. The process should be continued until the child no longer reacts to voice and the eyelash reflex in gone.

Among the inhalational anesthetics sevoflurane and halothane are used for induction of anesthesia. Sevoflurane and isoflurane have become the dominant maintenance anesthetics in children, displacing halothane because they are less soluble in blood and tissues than halothane. Desflurane is not used because it irritates the airway.

Sevoflurane is unique among the inhalational anesthetics, it is well tolerated when administered for induction of anesthesia, even without nitrous oxide in non premedicated children. The incidences of breath holding, coughing, laryngospasm, and desaturation during induction of anesthesia with sevoflurane and halothane are rare.[29]

Sevoflurane provides cardiovascular stability in children, when compared with other agents such as desflurane and halothane. Sevoflurane produces less increase in HR than isoflurane and less myocardial depression than halothane. Arrhythmias are also less common with sevoflurane when compared to halothane. The MAC of sevoflurane in neonates is 3.3%; in infants (aged 1 to 6 months), 3.2%; and in older infants (aged 6 to 12 months) and children (aged 1 to 12 years), 2.5%.[24]

An effective and safe method of inhalation induction for children is to give high flow of nitrous oxide and oxygen, 2:1, over the mouth and nose and the mask is slowly lowered onto the face with continuous monitoring of oxygen saturation. The patient will get the full effect of nitrous oxide within 1 to 2 minutes, as evidenced by the appearance of nystagmus and a regular and slower respiratory pattern of breathing. Then sevoflurane is added. There are three techniques of sevoflurane induction: (1) incremental increases in sevoflurane (2%, 4%, 6%, and 8%) in 100% oxygen, (2) a high concentration of sevoflurane

(8%) in O2, and (3) a high concentration of sevoflurane in the 1:1 mixture of N2O and O2.[29]

When halothane is used for induction, the concentration must be increased by 0.5% increments every 2 or 3 breathes. Concentrations of 3.5% to 4.0% halothane are considered proper limits for induction and should be reduced to 1.0% to 1.5% once anesthesia is established. [29]

Sevoflurane has a low blood-gas partition coefficient of 0.6 and is well tolerated by infants and children for inhalation induction. Children anesthetized with sevoflurane exhibited more rapid emergence and a significantly shorter postoperative recovery time compared with those receiving halothane.

Sevoflurane, even with the advantage of a low blood-gas solubility coefficient, has its own drawbacks, like postoperative agitation that especially occurs after short surgical procedures[29]. In addition, there have been reports of QT prolongation associated with sevoflurane anesthesia. But, with the cardiovascular stability and the lack of airway irritation that sevoflurane provides, the risk/benefit ratio of sevoflurane is much better than that of halothane.

Desflurane is not recommended for inhalation induction due to a high incidence of coughing and frequent and severe laryngospasm with significant

desaturation.[29] Laryngospasm is common with isoflurane anesthesia and more frequent and severe with desflurane anesthesia.

MAINTENANCE OF THE UPPER AIRWAY DURING INDUCTION

The pharyngeal airway is composed of collapsible soft tissues surrounded by bony structures (the mandible anteriorly and spinal column posteriorly). In the awake state, the pharyngeal airway is kept open by tonic and phasic contractions of pharyngeal dilator muscles contracting synchronously with contractions of the diaphragm with inspiration. During induction of anesthesia, airway obstruction occurs as the pharyngeal and laryngeal muscles are preferentially relaxed. In order to maintain the airway patent, the neck must be extended, the jaw thrust forward in a sniffing position, and the mouth open in case of nasal obstruction (the triple airway maneuver), with a moderate continuous positive airway pressure (CPAP; 10 to 15 cm H2O). It is therefore essential to establish an airtight system with the bag and mask and maintain CPAP to resist the collapsing force of relaxed upper airway until the patient is sufficiently anesthetized to tolerate the insertion of an oral airway without developing laryngospasm (Guedel's Stage 3, including the loss of intercostal muscle activities). Once the steady state of surgical anesthesia is achieved, CPAP of 5 to 10 cm H2O appears sufficient to maintain upper airway patency in spontaneously breathing children.[29]

Major causes of airway obstruction during induction of anesthesia are (1) preexistent nasal obstruction when the mouth is closed by the anesthesiologist; (2) obstruction of the oropharynx and/or nasopharynx by the relaxation of upper airway dilator muscles, and resultant collapse and/or posterior displacement of the tongue and (3) laryngospasm . Insertion of an oropharyngeal or nasopharyngeal airway usually solves the first and second problems, provided that the anesthesia is sufficiently deep to prevent pharyngeal reflex.

During sevoflurane anesthesia, an oropharyngeal airway is tolerated relatively early during induction compared with halothane. A nasopharyngeal airway is better tolerated even when the anesthesia is too light for insertion of an oropharyngeal airway; it should be well lubricated and inserted very gently to prevent mucosal injury and epistaxis.[29]

INTRAVENOUS INDUCTION

Intravenous induction has the advantage of faster induction and also elimination of the mask and its unpleasant odors when compared to inhalational route. The major disadvantage is the child's exaggerated fear of the needle and the difficulty of venipuncture. EMLA (eutectic mixture of local anesthetics 2.5% lidocaine and 2.5% prilocaine) cream seems to help alleviate this problem.

EMLA cream must be applied at least 1 hour prior to intravenous cannulation to provide sufficient dermal analgesia .[29]

PATHOPHYSIOLOGY OF EMERGENCE DELIRIUM

DEFINITION

Sikich and Lerman defined emergence delirium as “a disturbance in a child’s awareness of and attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate postanesthesia period.”[30]

It occurs within the first 30 min of recovery from anesthesia, is self-limited (5–15 min), and often resolves spontaneously

INCIDENCE

The incidence of emergence delirium in all postoperative patients is 5.3% . Incidence in children is (12-13*%).*

The incidence of emergence delirium after halothane, isoflurane, sevoflurane and desflurane ranges from 2-55%[2]. but may be as high as 80%.[27]

MEARSUREMENT SCALE

Cravero scale[2]

Pediatric anesthesia emergence delirium scale(PAED) [20]

Watcha scale

Ano’s four point scale[2]

Emergence Agitation scale[5]

Sedation-Agitation Scale (SAS) [9]

Richmond Agitation Sedation Scale (RASS).[19]

ETIOLOGICAL FACTORS [27]

- Rapid emergence
- Intrinsic characteristics of an anesthetic
- Postoperative pain
- Type of surgery
- Age- more common in children and elderly
- Preoperative anxiety
- Temperament of the child
- Adjunct medication like benzodiazepines

PATHOPHYSIOLOGY

The first sense to return during emergence from anesthesia is hearing, a sense that is made possible by the synapse between the acoustic thalamus and the lateral nucleus of the amygdala (LA) [27]. During post-anesthesia recovery, this connection is also responsible for auditory fear conditioning by exaggerating an inappropriate response to auditory stimuli.

Down regulation of large-conductance Ca^{2+}activated potassium channels - decrease in Ca2+ channels is associated with an increase in excitatory activity evoked by NMDA postsynaptic potentials at the thalamo-LA synapse, therefore enhancing stress induced behavior.

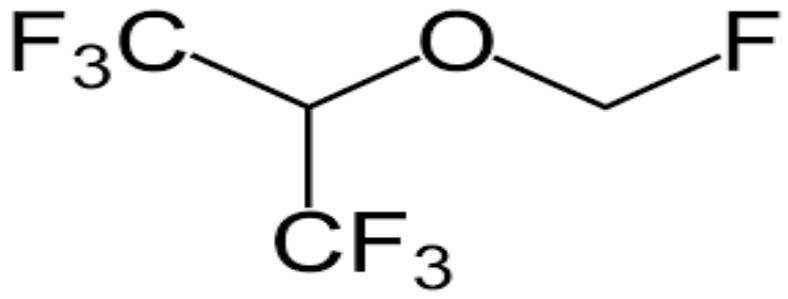
Postoperative emergence mimics Guedel Stage II (excitement stage) of anesthesia - pronounced slowing pattern on the electroencephalogram due to the interference of neurotransmitter metabolism and function within the central nervous system.

Specific excitation of the Locus Ceruleus neurons by inhalation anesthetics, especially sevoflurane, which ultimately plays an important role in this paradoxical excitation

Potentiation by sevoflurane of GABAergic depolarization/excitation in neocortical neurons[28].

PHARMACOLOGY OF SEVOFLURANE

Sevoflurane is polyfluorinated isopropyl methyl ether(1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane; fluoromethyl hexafluoro isopropyl ether



PHYSICAL PROPERTIES [31]

Non inflammable clear colourless liquid

Molecular weight- 200

Boiling point - 58.6

Saturated vapour pressure- 22.7 kpa at 20°c

MAC of sevoflurane is age dependentand ranges from 1.4 in elderly to 3.3 in neonates

In the presence of 65% N2O the MAC is - 0.7 to 2.0

Blood gas partition coefficient is 0.63 -0.69

Fat blood partition coefficient is 52

Oil gas partition coefficient is 47-54

It is stable and is stored in amber coloured bottles

UPTAKE AND DISTRIBUTION

It has a low blood/gas partition coefficient and therefore the rate of equilibration between alveolar and inspired concentrations is faster. It is non-irritant to the upper respiratory tract and therefore the rate of induction of anaesthesia is faster.

METABOLISM

Approximately 5% of the absorbed dose is metabolized in the liver to two main metabolites. The major breakdown product is hexafluoro isopropanol, an organic fluoride molecule which is excreted in the urine as a glucuronide conjugate. The second breakdown product is inorganic fluoride ion.

The metabolism of sevoflurane is catalysed by the 2E1 isoform of cytochrome P450. Sevoflurane metabolism does not result in the formation of trifluoroacetylated liver proteins and therefore cannot stimulate the formation of antitrifluoroacetylated protein antibodies

Sevoflurane is the least likely volatile anesthetic to form carbon monoxide on exposure to carbon dioxide absorbents.[31]

MODE OF ACTION

General anaesthetics appear to disrupt synaptic transmission especially in the area of ventrobasal thalamus. This mechanism may include potentiation of $GABA_A$ and glycine receptors and antagonism at NMDA receptors. Their mode of action at the molecular level appears to involve the expansion of hydrophobic

regions in the neuronal membrane, either with the lipid phase or within hydrophobic sites in the cell membranes.[31]

EFFECTS

CARDIOVASCULAR SYSTEM:

It has smaller effects on heart rate and cause less coronary vasodilatation.It decreases arterial pressure mainly by reducing peripheral vascular resistance, but cardiac output is well maintained. It causes mild myocardial depression resulting from its effect on calcium channels.It causes sensitization of the myocardium to exogenous catecholamines.It is a less potent coronary arteriolar dilator and therefore does not appear to cause 'coronary steal'. Sevoflurane is associated with lower heart rate and therefore helps to reduce myocardial oxygen consumption.[24]

RESPIRATORY SYSTEM:

Sevoflurane is a respiratory depressant causing dose dependent decreases in tidal volume and an increase in respiratory rate.It depresses the ventilator responses to CO2 and inhibits hypoxic pulmonary vasoconstriction.

It relaxes the bronchial smooth muscle constricted by histamine or acetylcholine.[24]

CENTRAL NERVOUS SYSTEM:

The principle effect of sevoflurane is general anaesthesia. It causes cerebral vasodilatation, leading to increase in cerebral blood flow .Cerebral

metabolic rate is decreased.It increases the intracranial pressure in a dose dependent manner.It is not associated with epileptiform activity.

GENITOURINARY:

Sevoflurane slightly decreases renal blood flow.It leads to increase in fluoride ion concentration. Renal toxicity does not appear to be related to inorganic fluoride concentrations due to rapid elimination from the body

HEPATIC :

Sevoflurane decreases portal vein blood flow, but increases hepatic artery blood flow, thereby maintaining total hepatic blood flow and oxygen delivery. It is generally not associated with immune-mediated anesthetic hepatotoxicity.

NEUROMUSCULAR :

Sevoflurane produces adequate muscle relaxation for intubation of children following an inhalation induction.

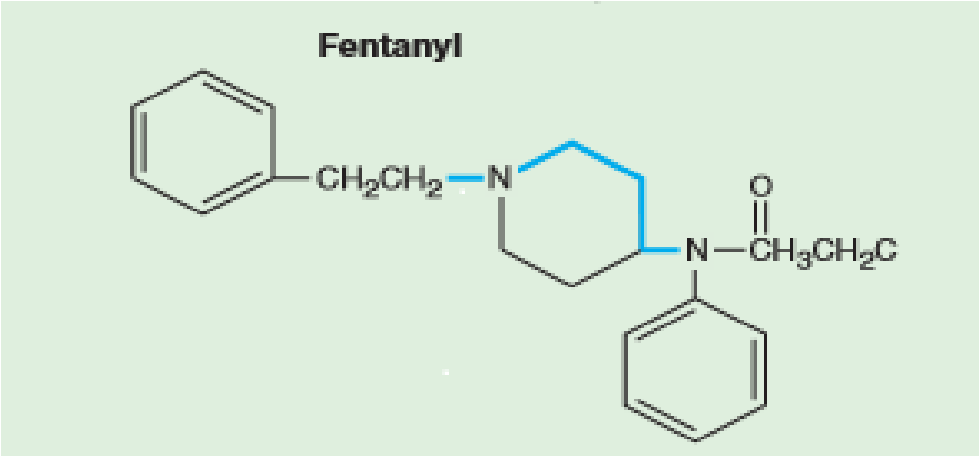
TOXICITY/SIDE EFFECTS

- Post Operative Nausea Vomitting
- Trigger agent for development of malignant hyperthermia
- Rapid emergence may lead to agitation in pediatric patients

PHARMACOLOGY OF FENTANYL

Fentanyl is a phenyl piperidine-derivative synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is 75 to 125 times more potent than morphine.

Chemical structure- tertiary amine which is a synthetic phenylpiperidine derivative



PHYSICAL PROPERTIES [31]

Available as

- Clear colourless solution for injection
- Transdermal patch
- Sublingual tablets
- Lozenges
- Iontophoretic transdermal system

pKa of fentanyl is 8.4

9% unionized at a pH of 7.4

Molecular weight- 286

Highly lipid soluble

Octanol water partition coefficient – 717

MECHANISM OF ACTION

Fentanyl is highly selective mu agonist, mu receptor appears to be specifically involved in the mediation of analgesia.Opiods appear to exert their effects by interacting with presynaptic Gi protein receptors,leading to hyperpolarisation of cell membrane by increasing K+ conductance.Inhibition of adenylate cyclase,leading to reduced production of cAMP and closure of voltage sensitive calcium channels occurs.The decrease in membrane excitability that results may decrease both pre and post synaptic responses [31]

ROUTE OF ADMINISTRATION/ DOSES

Premedication - intramuscular route -50 to 100 µgm

Anesthetic induction is usually achieved by combining a loading dose of fentanyl (2 to 6 µg/kg) with a sedative-hypnotic, most commonly thiopental or propofol, and a muscle relaxant.

Maintenance of anesthesia can be achieved with N2O (60% to 70%) in O2, low concentrations of potent inhaled anesthetic agents, and additional fentanyl (intermittent boluses of 25 to 50 µg every 15 to 30 minutes or a constant infusion of 0.5 to 5.0 µg/kg/hour).

Epidural route – 50 to 100 µgm

As an adjuvant in spinal anesthesia- 5-25 µgm

The drug acts rapidly in 2-5 minutes due to its rapid lipid solubility when administered intravenously. Small doses have duration of action of 30-60 minutes whereas high doses may be effective for 4-6 hrs.

Transdermal fentanyl patch-serum fentanyl concentration increases gradually with equilibrium occurring between 12-24 hrs.It should be replaced every 72 hrs

Iontophoretic transdermal system devices should be replaced or stopped after 24 hrs[31]

EFFECTS

CARDIOVASCULAR SYSTEM:

The most significant effect is bradycardia of vagal origin. Cardiac output,mean arterial pressure,systemic and pulmonary vascular resistance

remain unaffected.It obtunds the cardiovascular response to laryngoscopy and intubation.

RESPIRATORY SYSTEM:

It is a potent respiratory depressant causing a decrease in both respiratory rate and tidal volume.It diminishes the ventilator response to hypoxia and hypercarbia. It is a potent antitussive agent. Fentanyl causes chest wall rigidity- wooden chest phenomenon may occur due to its effect on mu receptors located on the GABAergic interneurons. It causes minimal histamine release ,so bronchospasm is rare

CENTRAL NERVOUS SYSTEM:

Fentanyl is 50-80 times more potent an analgesic than morphine and has little sedative and hypnotic property. Miosis is produced due to the stimulation of Edinger Westphal nucleus. Opioids reduce cerebral oxygen consumption, cerebral blood flow, cerebral blood volume, and intracranial pressure.Large doses of Fentanyl may rarely cause seizure like motor activity. No epileptic spike wave patterns are demonstrable in EEG. Stimulation of the medullary chemoreceptor trigger zone is responsible for opioid-induced nausea and vomiting[24]

GASTRO INTESTINAL:

Decreases gastro intestinal motility and decreases gastric acid secretion.Biliary colic may result from opioid-induced contraction of the sphincter of Oddi

ENDOCRINE:

Fentanyl obtund the metabolic stress response to sugery by decreasing the secretion of stress hormones like catecholamines and cortisol. It does not increase the activity of ADH.

TOXICITY/SIDE EFFECTS

- Respiratory depression- due to the appearance of secondary peak in the plasma fentanyl concentration due to elution from the muscle
- Nausea and vomiting
- Dependence

PHARMACOKINETICS

ABSORPTION:

Fentanyl is absorbed orally and has a bioavailability of 33%.Orally administered fentanyl becomes highly ionized in the stomach(99.9%),leading to slow absorption in the small bowel and subsequent first pass metabolism

DISTRIBUTION:

Fentanyl is 81-94% bound to plasma proteins

Vd is 0.88-4.41 l/kg.

Short duration of action of single dose of drug is due to redistribution, whereas continuous infusion may lead to saturation of tissues and prolonged duration of action.

It is more lipid soluable, crosses the blood brain barrier easily and has faster onset of action.

Intrathecal fentanyl does not cause delayed respiratory depression ,as due to its high lipid solubility,it is rapidly absorbed in the spinal cord.

METABOLISM:

Fentanyl is metabolized primarily by N-deaklylation to norfentanyl with subsequent hydroxylation to hydroxy propionyl derivatives. It also undergoes hydroxylation and amide hydrolysis. Cytochrome P450 3A plays predominant role.

EXCRETION:

10% of administered dose is excreted in urine.

Clearance -13ml/kg/min.

Elimination half life-141-853 minutes.

Halothane decreases the clearance of fentanyl by 48%.

Clearance of fentanyl is decreased in patients with renal and hepatic impairment.

DRUG INTERACTION

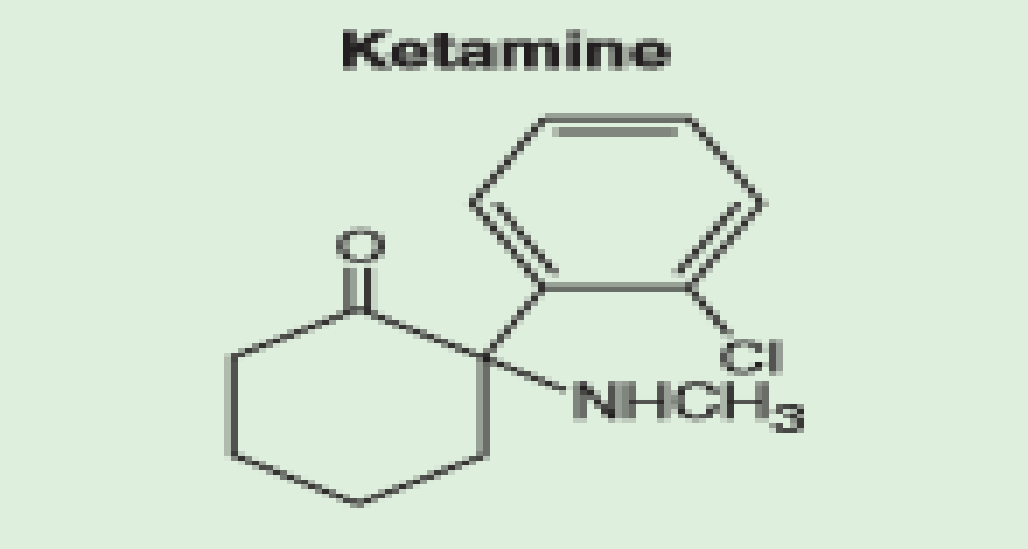
Fentanyl decreases the apparent MAC of coadministered volatile agents

Increases the effect of non depolarizing muscle relaxant

PHARMACOLOGY OF KETAMINE

Ketamine is a structural analogue of phencyclidine-

2-(0-Chlorophenyl)-2-(methylamino)-cyclo-hexanone hydrochloride



PHYSICAL CHARACTERISTICS[31]

Ketamine is soluble in water and is presented as solutions of 10 mg/ kg racemic ketamine containing sodium chloride to produce isotonicity, and 50 or 100 mg/ kg in multidose vials which contain benzethonium chloride 0.1 mg /kg as preservative.

The pH of the solutions is 3.5-5.5.

The pKa of ketamine is 7.5.

The racemic mixture contains in equal proportions two enentiomers due to its chiral centre of cyclo-hexanone ring ([S-(+)-ketamine] and [R-(-)-ketamine]).

MECHANISM OF ACTION

Ketamine is a non competitive antagonist of NMDA receptor Ca2+ channel pore and also inhibits NMDA receptor activity by interaction with the phencyclidine binding site.

Inhibition of glutamate gated NMDA receptors by ketamine provides a mechanism of a predominant analgesic profile.It reduces the presynaptic release of glutamate in addition to complex interactions with opiod receptors.

It acts as an antagonist at monoaminergic, muscarinic and nicotinic receptors

It has local anesthetic activity at high doses which may be due to sodium channel inhibition

Ketamine functionally “dissociates” the thalamus (which relays sensory impulses from the reticular activating system to the cerebral cortex) from the limbic cortex (which is involved with the awareness of sensation)

S-(+)-ketamine has four times greater affinity for the NMDA receptor than R-(-)-ketamine.It is twice as potent as the racemic mixture and three times as potent as the R(-) form.[31]

ROUTE OF ADMINISTRATION /DOSES

Induction of anesthesia

Intramuscular route- 4-10mg/kg; onset of action- 2-8 minutes;duration of action-10-20 minutes

Intravenous route-0.5-2 mg/kg administered over a period of 60 seconds;onset of action-30 seconds; duration of action 5-10 minutes.

Maintenance of anaesthesia

Intravenous infusion at a rate of 10-50µgm/kg

Sedation and analgesia

Intramuscular dose- 2-4mg/kg

Intravenous dose-0.2-0.75mg/kg; followed by an infusion of 5-20µgm/kg/min.

Ketamine may also be administered orally, rectally, nasally, intrathecally or extradurally.

When used neuraxially preservative free solution must be used.[31]

EFFECTS

CARDIOVASULAR SYSTEM:

Ketamine increases arterial blood pressure, heart rate and cardiac output due to central stimulation of the sympathetic nervous system and inhibition of the reuptake of norepinephrine after release at the nerve terminals. It increases the pulmonary artery pressure and myocardial work; these effects masks the direct myocardial depressant of ketamine. Baroreceptor function is well maintained

RESPIRATORY SYSTEM:

Ventilatory drive is minimally affected. Ketamine is a bronchial smooth muscle relaxant R(-) isoform is more potent and S(+) isoform has minimal effect.So racemic mixture is most suitable for bronchospasm. It improves pulmonary compliance. Airway reflexes are preserved but there is increased risk of aspiration in full stomach patients.Increased salivation associated with ketamine can be attenuated by premedication with an anticholinergic agent such as glycopyrrolate.

CENTRAL NERVOUS SYSTEM:

It increases the cerebral oxygen consumption, cerebral blood flow, intracranial pressure and intraocular pressure. The dissociative state is produced

by separation functionally and electrophysiologically of the thalamo cortical and limbic system. The eyes remain open; pupillary dilatation,nystagmus and hypertonus occurs.Visceral pain is poorly obtunded. EEG demonstrates dominant theta activity with loss of alpha rhythm. S(+) ketamine has faster recovery.

AUTONOMIC NERVOUS SYSTEM:

Salivary secretions are increased; gastric motility is unaffected.

GENITOURINARY SYSTEM:

It increases the uterine tone.

METABOLIC/OTHERS:

Circulating levels of adrenaline and noradrenaline are increased. It reduces leucocyte activation during sepsis or hypoxemia.

TOXICITY/SIDE EFFECTS:

- Post Operative Nausea Vomitting
- Emergence delirium, unpleasant dreams, hallucinations
- Transient rash
- Pain on injection

PHARMACOKINETICS[31]

ABSORPTION:

Bioavalibity: oral- 20-25%;nasal- 25-50%; intramuscular-93%.

Peak plasma levels are usually achieved within 10–15 min after intramuscular injection.

DISTRIBUTION:

Ketamine is more lipid soluble and less protein bound- leading to rapid brain uptake and subsequent redistribution. Distribution half-life is 10–15 min**.**

Awakening is due to redistribution from brain to peripheral compartments.

METABOLISM:

Ketamine is metabolized in the liver by N-demethylation and hydroxylation via cytochrome P 450 enzyme system of the cyclohexylamine ring. Norketamine is a metabolite which is 30% as potent as ketamine and is metabolized to inactive glucuronide.Extensive hepatic uptake (hepatic extraction ratio of 0.9) explains ketamine's relatively short elimination half-life (2 h).

EXCRETION:

The conjugated metabolite are excreted in the urine

REVIEW OF LITERATURE

Sevoflurane is a popular inhaled anesthetics widely used for induction and maintanence of anesthesia in pediatric age group.The major concern with sevoflurane anesthesia is its association with emergence delirium in children. Several studies were conducted in the past comparing various agents to reduce the incidence and severity of emergence delirium.

Ashraf Arafat et al (2016) [3] conducted a study on 120 children undergoing tonsillectomy surgery from sevoflurane anesthesia. They divided them into three groups ,group F receiving 1µgm/kg , group K receiving 0.5 mg/kg of ketamine 10 mins before the end of the surgey and group C as control. They observed that the incidence of emergence delirium was significantly low in both fentanyl and ketamine group when compared to the control group with no significant difference between both the groups. There was also no significant difference regarding recovery and discharge times from post-anesthesia care unit. There were no significant differences in Children's Hospital of Eastern Ontario Pain Scale. The incidence of nausea or vomiting was significantly more in fentanyl group compared to that in other two groups.

Manal et al(2014) [25] perfomed a study to compare the effect of intravenous injection of small dose of propofol, fentanyl or ketamine at the end of surgery, just before the discontinuation of sevoflurane on the incidence and

severity of sevoflurane emergence agitation in children undergoing hypospadias repair operations. They observed that the incidence of emergence agitation was significantly lower in propofol and fentanyl group when compared to ketamine and control group. The time for awakening was significantly prolonged in propofol, ketamine and fentanyl group , while PACU duration was significantly prolonged in fentanyl group. No significant complications occurred except a significantly higher incidence of vomiting in fentanyl group.

Kim et al (2016)[21] did a study on paediatric patients (2–6 years old) undergoing ophthalmic surgery where they received premedication with either 0.1mg/kg midazolam or 1mg/kg ketamine and they observed that the incidence of emergence delirium was significantly lower in the ketamine group than the midazolam group. There was no significant difference in overall incidence of emergence delirium. The frequency of midazolam used as rescue medication was significantly lower in the ketamine group than in the midazolam group.

M.S.Kim et al (2013)[26] designed a study to compare the effect of fentanyl and propofol on pediatric patients receiving sevoflurane anesthesia on the incidence of emergence delirium and they observed that the incidence of emergence delirium is lower in both propofol and fentanyl group when compared to control group with no significant difference between both the groups.the incidence of nausea and vomiting is more in fentanyl group.

Fentanyl and propofol group have longer duration of stay in PACU when compared to control group with no difference between both the groups.

Dahmani S et al (2010)[11] observed in a meta analysis that propofol, ketamine, fentanyl, and preoperative analgesia had a prophylactic effect in preventing emergence delirium. The analgesic properties of these drugs do not seem to have a role in this effect.(18)

Dalens BJ et al (2006) [12] conducted a study for pediatric cerebral magnetic resonance imaging with small doses of ketamine or nalbuphine administered just before discontinuing sevoflurane anesthesia for prevention of emergence delirium. They observed that the incidence of emergence delirium is low in Ketamine and Nalbuphine group when compared to the control group. Incidence of emergence delirium in Nalbuphine group is low than that of Ketamine group.

Woon Young Kim et al (2010) [23] observed the effect of two different doses of Ketamine on the incidence of emergence agitation in children undergoing tonsillectomy and adenoidectomy under sevoflurane general anesthesia and concluded that the incidence of emergence delirium and CHEOPS is low in ketamine group when compared to control group with no difference between the groups receiving 0.5 mg/kg of ketamine at the end of surgery and 1mg/kg of ketamine at the beginning of surgery .Extubation time in

ketamine group receiving 0.5 mg/kg at the end of surgery was significantly prolonged compared with ketamine group receiving 1mg/kg at the beginning of surgery and the control group.

MATERIALS AND METHODS

The study was carried out in the ENT Department, Kanyakumari Government Medical College after obtaining institutional ethical committee approval and written informed consent from patients.

Aim of the Study:

The present work is to compare the effect of fentanyl vs ketamine on the incidence emergence delirium from sevoflurane anesthesia in pediatric patients undergoing tonsillectomy .

Study Design:

Prospective, randomized, double blinded study

The study was started after receiving Institutional Ethical Committee approval and written informed consent from all the patients.

Randomization:

Simple randomized sampling was done by computer generated random numbers.

Sample Size:

The sample size is calculated using this formula

$$N = \frac{2 \times \{z(1-\alpha/2) + z(1-\beta)\}2}{D2}$$

where z (1- a /2) is the alpha error whose value for confidence level of 99.9% (error of 0.1%) , is 3.2905 and z(1- b) is the beta error or power of the study whose value for power of 95 % is 1.6449

$$D = \frac{\text{Difference in means}}{S.D}$$

However for the sake of greater accuracy, it was decided to take 20 cases in each group.

Forty patients were studied, randomized into two groups of 20 each.

Group allocation:

Patients were allocated into two groups

Group F (n= 20) : Patients receiving Fentanyl

Group K (n= 20) : Patients receiving Ketamine

BLINDING:

Study drugs are prepared by an anesthesiologist not involved in the study. Anesthesiologist who observe the patient is unaware of the study group until the end of the study.

INCLUSION CRITERIA:

(I) Age 5 to 12 years

(II) ASA l &ll

(III) Written informed consent

EXCLUSION CRITERIA:

(I) Patient refusal

(II) ASA grade III and IV

(III) Patients with h/o sleep apnoea

(IV) Cognitive or developmental disorder

(V) Patients on sedative medication

(VI) Neurological condition that may limit patient's ability to communicate with or understanding nursing personnel.

(VII) Patients requiring additional dose of muscle relaxant

Materials

- Drugs for the study
- Monitor – Philips Sure Signs VM8 – ECG, Pulse Oximeter, Non Invasive Blood Pressure, Capnograph.
- Equipment & drugs for resuscitation

Methods

Pre Operative Preparation:

The patients were pre operatively assessed; their parents were explained about the purpose of the study and about the possible adverse events that can occur due to the study drug, and written informed consent was obtained from those parents who were willing to allow their ward to take part in the study.

Conduct of Anaesthesia:

On arrival of the patient in the operating room, monitors – Pulse oximeter, Non Invasive Blood Pressure (NIBP) and ECG were connected and baseline values were recorded.

IV access is established

Patient is premedicated with Inj Atropine 15µ/kg, Inj Fentanyl 2µ/kg, Inj. Midazolam 0.15mg/kg. Anesthesia is induced with sevoflurane in 100% oxygen (6 L/min) through a facemask, with a gradual increase of sevoflurane concentration with every single breath to a maximum of 8 vol%.

Inj.Dexamethasone 0.3mg/kg and Inj.Ondansetron 0.1mg/kg iv is given after induction. Tracheal intubation is facilated with Inj.Atracurium 0.5 mg/kg. General anesthesia is maintained with O2 and N2O 50:50, sevoflurane 1% with controlled ventilation. Paracetamol suppository 15mg/kg is kept after induction.

Before the start of surgery,the surgeon infiltrates the operative site with 1% lidocaine for pain control.

The study drug is prepared and diluted to 5ml by an anaesthesiologist not participating in the study

In **GROUP F**, patients received 1µg/kg of fentanyl 10 min before the end of surgery, (n=20).

In **GROUP K**, patients received 0.5mg/kg of ketamine 10 min before the end of surgery, (n=20).

Intra operatively hemodynamic variables like heart rate, blood pressure, oxygen saturation, EtCO2

The study drug is given by the anesthesiologist not participating in the study 10 minutes before the end of the surgery

At the end of surgery, once hemostasis is achieved, the inhalational anesthetics is discontinued and patient is ventilated with 100% oxygen at 6 L/min.

After onset of spontaneous respiration ,the neuro muscular blockade is reversed with Inj.Neostigmine 0.05mg/kg and Inj.Atropine 20 µg/kg.

After thorough oropharyngeal suctioning ,after return of sufficient spontaneous breathing, gag reflex,facial grimaces and purposeful motor movements, patient is extubated and put in recovery position

PARAMETERS MONITERED

EMERGENCE TIME is defined as the time of first response to command or eye opening on command after discontinuation of inhalational anesthetics.

TIME TO EXTUBATION is defined as time from the end of surgery to tracheal extubation .

DURATION OF SURGERY is recorded as the time between the insertion and removal of the mouth gag .

DURATION OF ANESTHESIA is recorded as the time from induction until the extubation.

All patients were observed continuously for at least 30 min post operatively.

The **primary outcome** of the study is the incidence of post-operative emergence delirium, which is assessed every 5 min during the first 30 min using **Aono''s four point scale** as follows:

(1) Asleep

(2) Awake but calm

(3) Agitated but consolable

(4) agitated and difficult to console

Grades 1 and 2 in the scale of behavior are considered as no agitation and Grades 3 and 4 are considered the presence of agitation

The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) based on crying, facial expression, verbal statements, position of torso, touching of the wound and movement of legs is used for post-operative pain assessment and it is measured at 5, 10, 20 and 30 min post-operatively

1.CRY	
No cry	1
Moaning	2
Crying	3
screaming	4
2.FACIAL	
Smiling	0
Composed	1
grimace	2
3.VERBAL	
Positive	0
None	1
Complaints other than pain	1
Pain complaints	2
Pain & non pain compliants	2
4.TORSO	
Neutral	1
Shifting	2
Tense	2
Shivering	2
Upright	2
restrained	2
5.TOUCH	
Not touching	1
Reach	2
Touch	2
Grab	2
restrained	2
6.LEGS	
Neutral	1
Squimming,kicking	2
Draw up tensed	2
Standing	2
restarined	2
Minimum score – 4 **Maximum score – 13**	

Discharge criteria

1. being fully awake,
2. stable vital signs for 30 min,
3. no bleeding,
4. no pain,
5. no nausea or vomiting and
6. able to ambulate according to age

Children were considered ready for discharge from the recovery room when the **modified Aldrete post-anesthesia score** is ≥9.[4]

TIME TO RECOVERY is recorded as the time from extubation to reach the modified aldrette score of > 9

Patients who fulfill the discharge criteria are transferred to PACU and the recovery room stay time is recorded.

Adverse events

1. vomiting
2. oxygen desaturation
3. somnolence and
4. hallucination incidence are also recorded

MODIFIED ALDRETE POST-ANESTHESIA SCORE

Parameter	Description of patient	Score
Activity level	Moves all extremities voluntarily/on command	2
	Moves 2 extremities	1
	Cannot move extremities	0
Respirations	Breathes deeply and coughs freely	2
	Is dyspneic, with shallow, limited breathing	1
	Is apneic	0
Circulation (blood pressure)	Is 20 mm Hg > preanesthetic level	2
	Is 20 to 50 mm Hg > preanesthetic level	1
	Is 50 mm Hg > preanesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level >90% when breathing room air	2
	Requires supplemental oxygen to maintain level >90%	1
	Has level <90% with oxygen supplementation	0

Maximum total score is 10; a score of ≥9 is required for discharge.

OBSERVATION AND RESULTS

The data collected from all the selected cases were recorded and tabulated in a Master Chart.

Statistical Tools:

Statistical analysis was performed with the help of statistical package IBM-SPSS version 20.0 (IBM-SPSS Science Inc., Chicago, IL).

Baseline characteristics of both the groups were tabulated by descriptive statistics (mean , standard deviation) and frequency table.

Continuous data were compared by Independent sample t test

Chi square test was used to find out association between collected categorical data.

Significance was defined by *P* values less than 0.05

RESULTS

GROUP F : Fentanyl group

GROUP K : Ketamine group

A: DEMOGRAPHIC DATA

Table A1: Age Distribution (years)

PARAMETER	GROUP F	GROUP K
MEAN	9.45	9.00
STD DEVIATION	2.01	2.38
P VALUE	0.523	

The two groups are matched according to their weight and found that both groups are comparable (9.45± 2.01 in fentanyl group vs 9.00±2.38 in ketamine group) and the datas are statistically not significant with a p value 0.523.

($p > 0.05$)

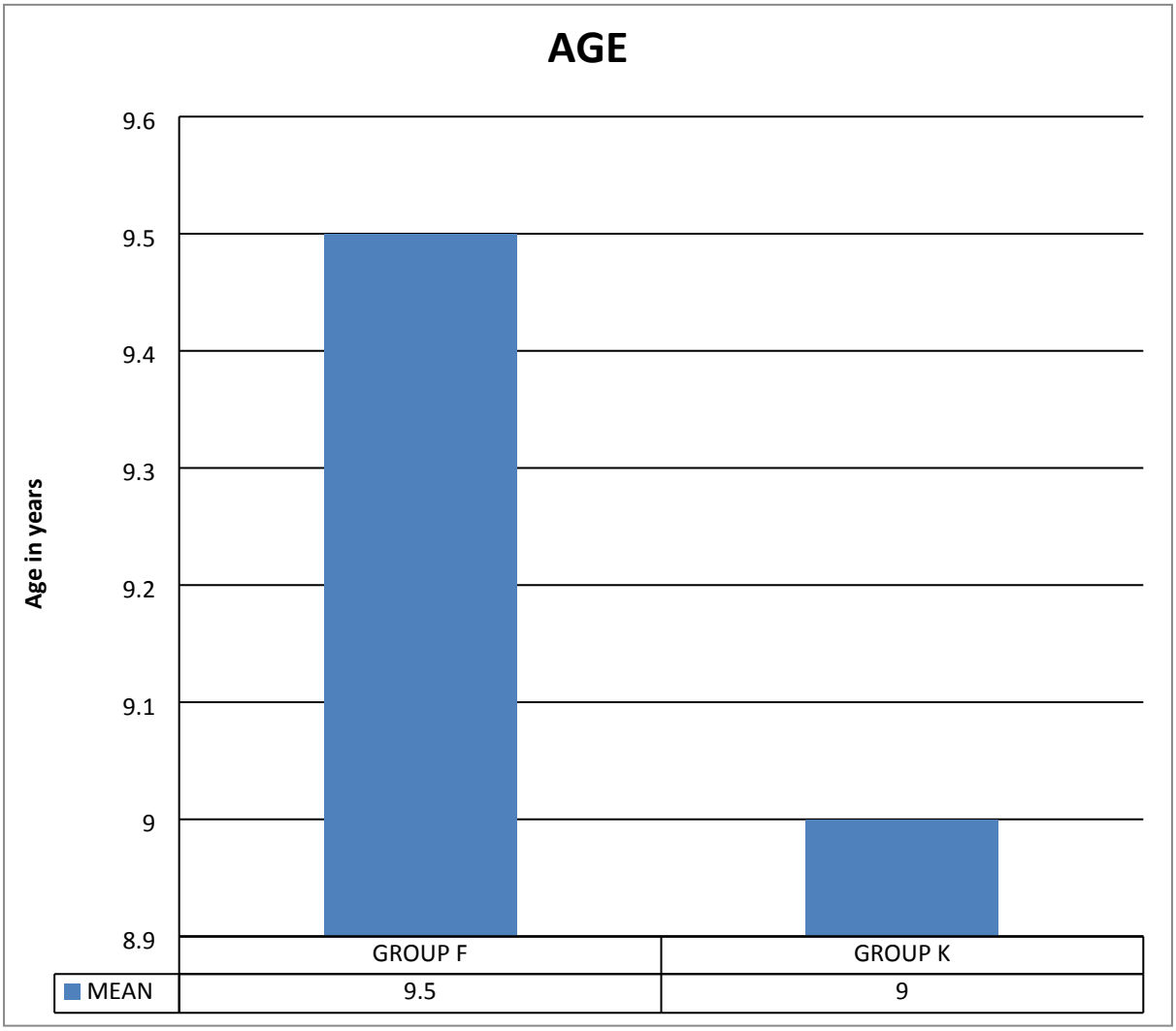

AGE
Age in years
9.6
9.5
9.4
9.3
9.2
9.1
9
8.9
GROUP F
GROUP K
MEAN
9.5
9

Table A2: Weight(kg)

PARAMETER	GROUP F	GROUP K
MEAN	25.55	23.95
STD DEVIATION	6.86	6.09
P VALUE	0.44	

The two groups were matched according to their weight and found that both the groups are comparable (25.55±6.86 in fentanyl group vs 23.95±6.09 in ketamine group) and the datas are statistically not significant with a p value 0.44.($p > 0.05$).

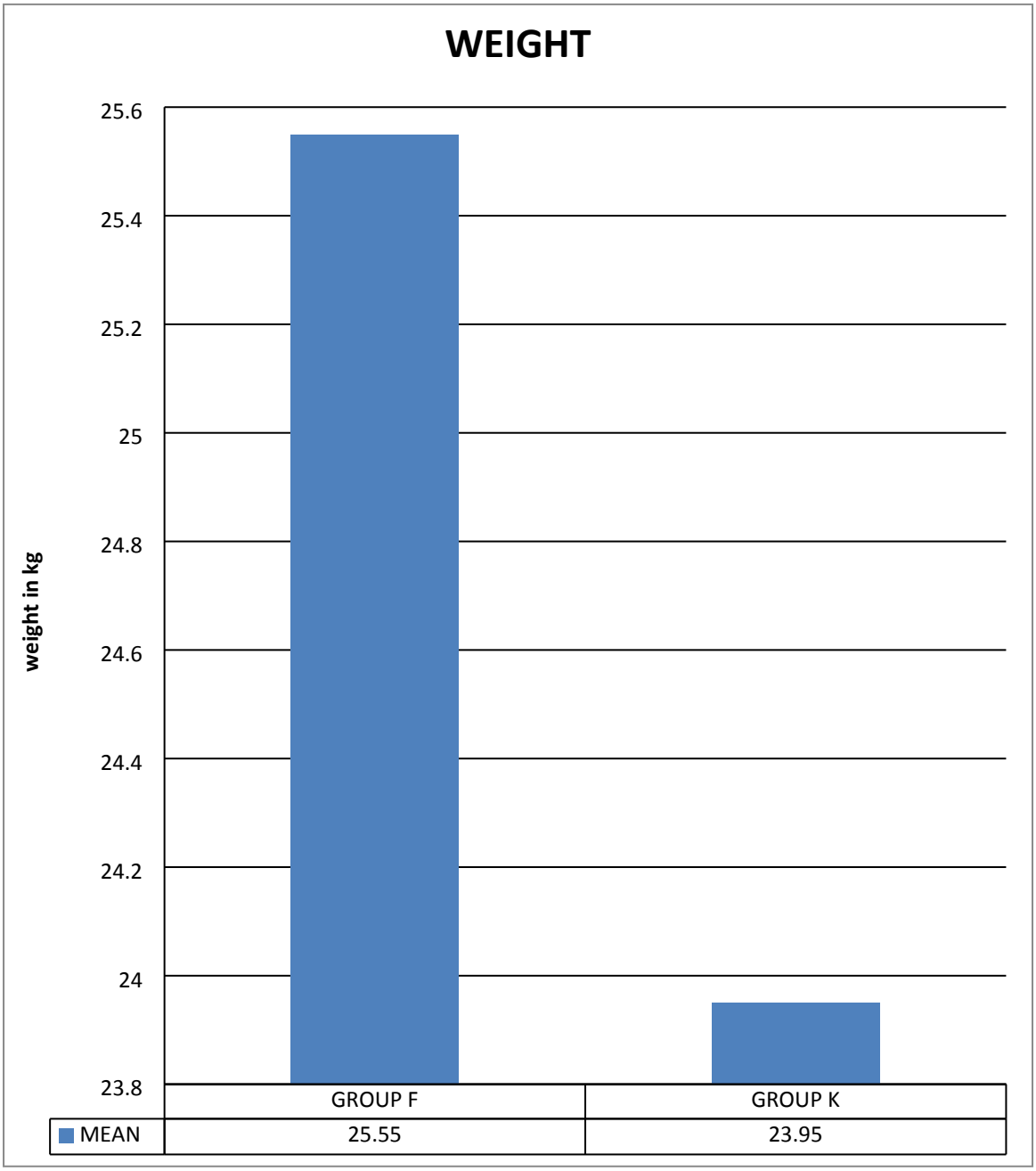

WEIGHT
weight in kg
25.6
25.4
25.2
25
24.8
24.6
24.4
24.2
24
23.8
GROUP F
GROUP K
MEAN
25.55
23.95

Table A3: Duration of Surgery (minutes)

DURATION OF SURGERY is recorded as the time between the insertion and removal of the mouth gag .

PARAMETER	**GROUP F**	**GROUP K**
MEAN	32.95	31.65
STD DEVIATION	7.39	5.16
P VALUE	0.523	

The two groups were matched according to the duration of surgery and found that they are comparable (32.95±7.39 in fentanyl group vs 31.65±5.16 in ketamine group) and the datas are statistically not significant with a p value of 0.523. ($p>0.05$)

DURATION OF SURGERY

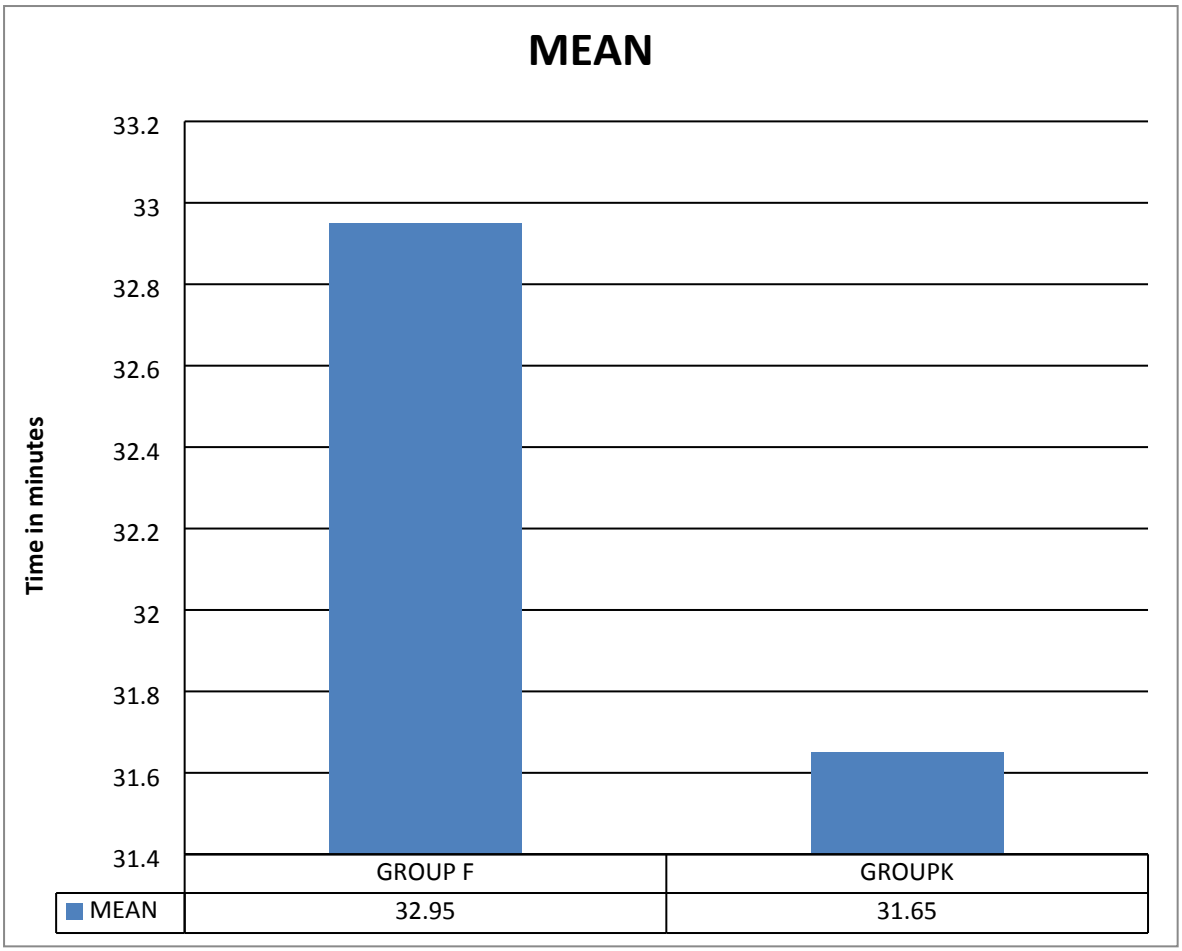


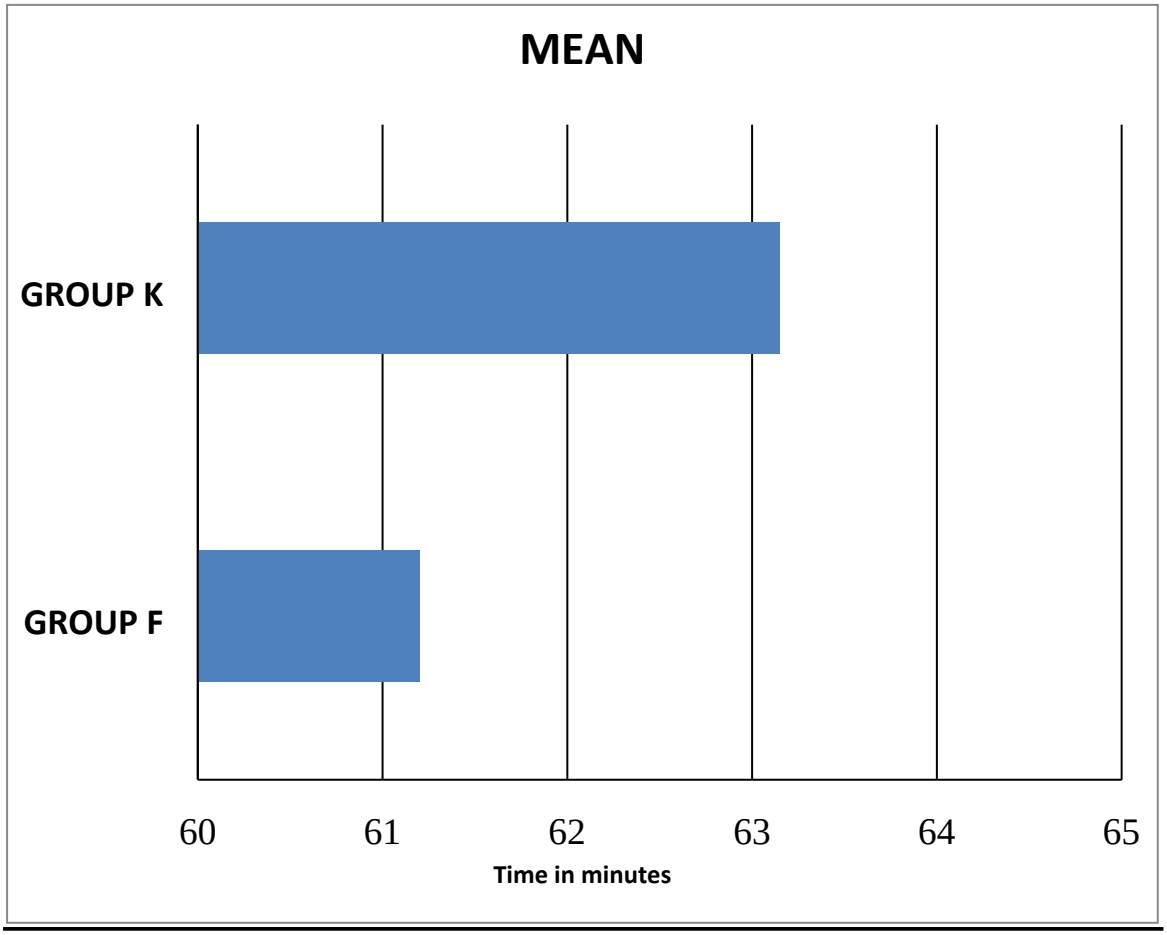
TABLE A4: DURATION OF ANESTHESIA (MINUTES)

DURATION OF ANESTHESIA is recorded as the time from induction until the extubation.

PARAMETER	GROUP F	GROUP K
MEAN	61.20	63.15
STD DEVIATION	8.67	11.24
P VALUE	0.543	

The two groups were matched according to the duration of Anesthesia and found that they are comparable (61.20±8.67 in fentanyl group vs 63.15±11.24 in ketamine group) and the datas are statistically not significant with a p value of 0.543. ($p>0.05$)

DURATION OF ANESTHESIA



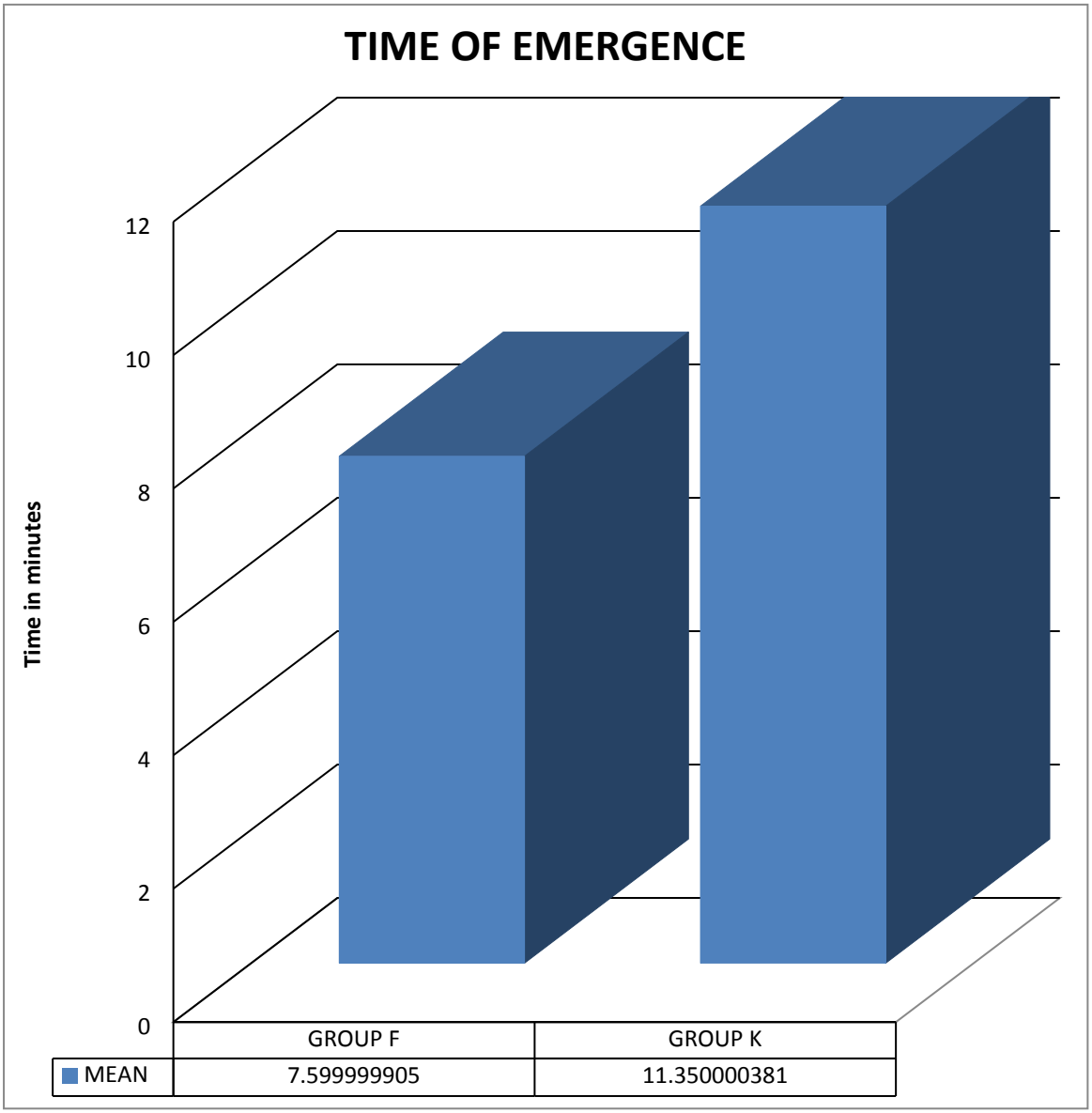
	GROUP F	GROUP K
MEAN	61.20	63.15

B.TIME OF EMERGENCE

EMERGENCE TIME is defined as the time of first response to command or eye opening on command after discontinuation of inhalational anesthetics

PARAMETER	**GROUP F**	**GROUP K**
MEAN	7.60	11.35
STD DEVIATION	3.52	3.48
P VALUE	0.002	

The two groups were matched according to the time of emergence and found that there was significant difference in their mean values (7.60±3.52 in fentanyl group vs 11.35±3.48 inketamine group) and the datas are statislly significant with a p value of 0.002. ($p>0.05$)

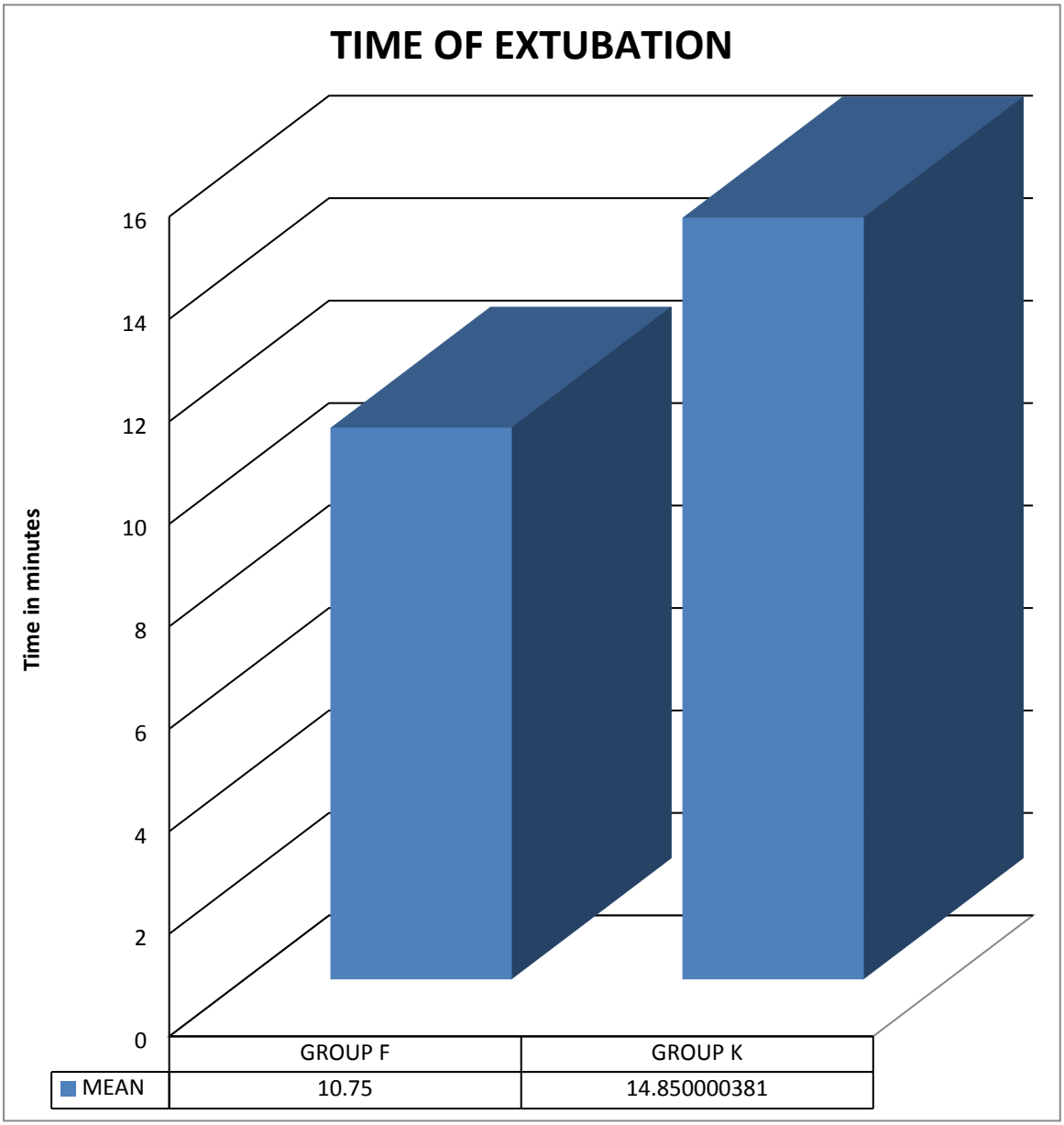

TIME OF EMERGENCE
Time in minutes
12
10
8
6
4
2
0
GROUP F
GROUP K
MEAN
7.599999905
11.350000381

C.TIME OF EXTUBATION

TIME TO EXTUBATION is defined as time from the end of surgery to tracheal extubation .

PARAMETER	GROUP F	GROUP K
MEAN	10.75	14.85
STD DEVIATION	3.32	4.38
P VALUE	0.002	

The two groups were matched according to the time of extubation and found that there is significant difference in their mean values (10.75±3.32 in fentanyl group vs 14.85±4.38 in ketamine group) and the datas were statistically significant with a p value of 0.002. ($p>0.05$)

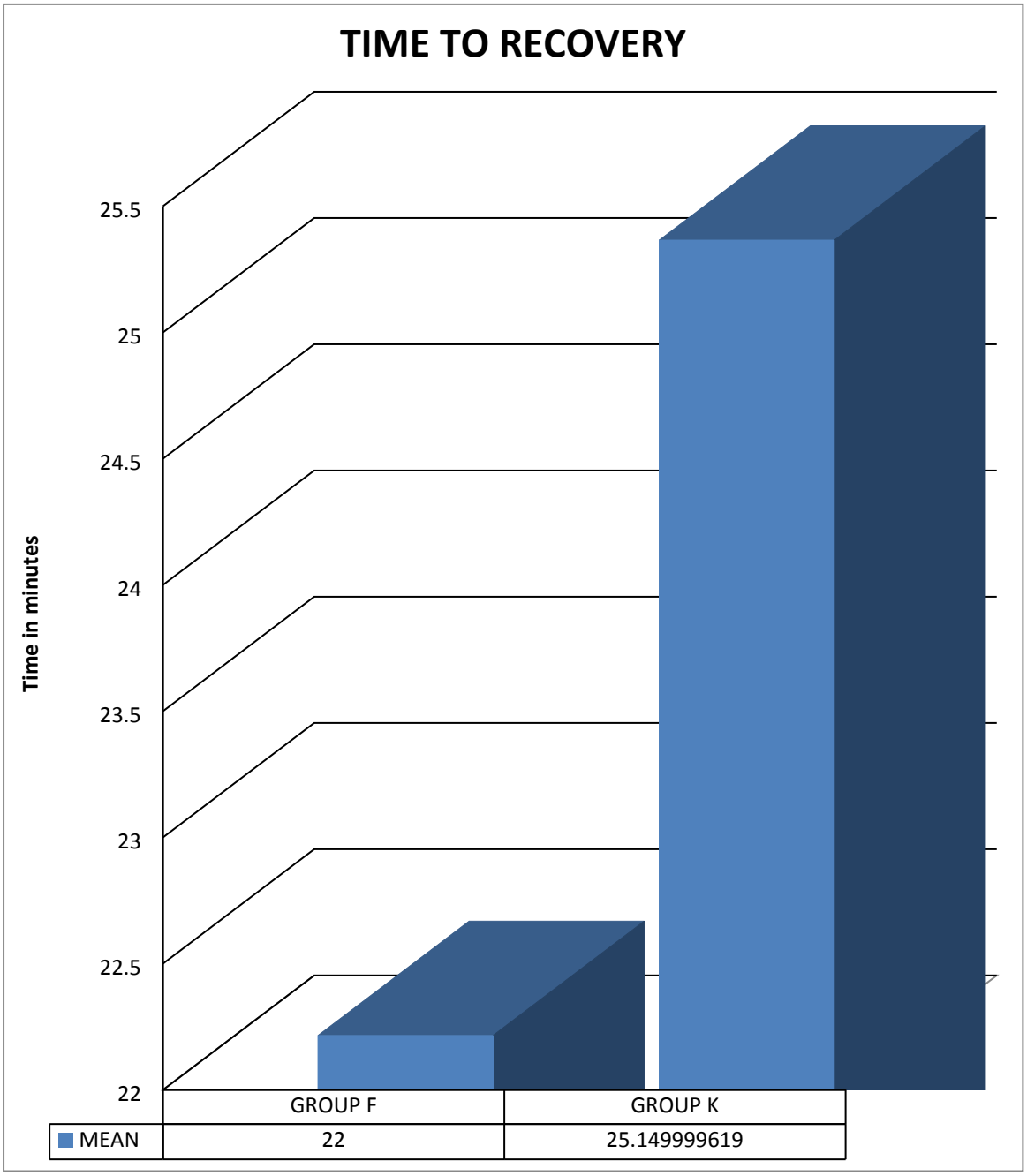

TIME OF EXTUBATION
Time in minutes
16
14
12
10
8
6
4
2
0
GROUP F
GROUP K
MEAN
10.75
14.850000381

D.TIME TO RECOVERY

TIME TO RECOVERY is recorded as the time from extubation to reach the modified aldrette score of > 9

PARAMETER	GROUP F	GROUP K
MEAN	22.00	25.15
STD DEVIATION	2.38	3.39
P VALUE	0.002	

The two groups were matched according to the time to recovery and found that there is significant difference in their mean values (22.00±2.38 in fentanyl group vs 25.15±3.39 in ketamine group) and the datas are statistically significant with a p value of 0.002.(p>0.05)

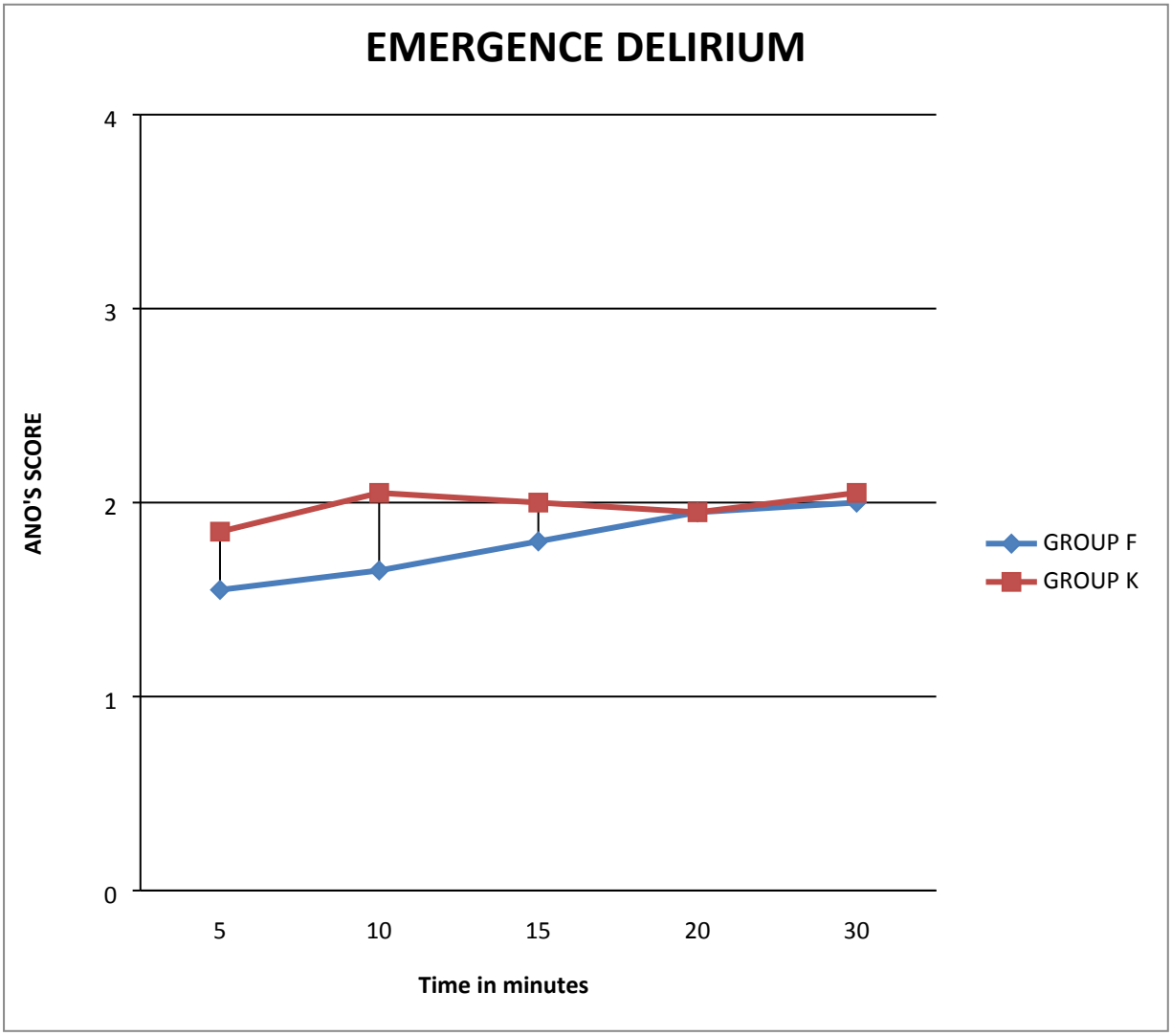

TIME TO RECOVERY
Time in minutes
25.5
25
24.5
24
23.5
23
22.5
22
GROUP F
GROUP K
MEAN
22
25.149999619

E.EMERGENCE DELIRIUM

Emergence delirium was assessed using Ano's four point scale at 5,10,15,20 and 30 minutes. The score of 3 and 4 are considered as presence of emergence delirium.

TIME (min)	GROUP	MEAN	STD.DEV	P VALUE
ANO_5	F	1.55	0.83	
	K	1.85	0.99	0.304
ANO_10	F	1.65	0.75	
	K	2.05	0.94	0.145
ANO_15	F	1.80	0.41	
	K	2.00	0.65	0.251
ANO_20	F	1.95	0.22	
	K	1.95	0.51	1.000
ANO_30	F	2.00	0.00	
	K	2.05	0.22	0.324

The two groups were matched according to the emergence delirium occurrence by Ano's four point scale and found that they were statistically not significant at all times. The mean values in both groups are less than 2 and the p value is >0.05 at all times.



	MEAN				
TIME(min)	5	10	15	20	30
GROUP F	1.55	1.65	1.8	1.95	2
GROUP K	1.85	2.05	2	1.95	2.05

F.CHEOPS (Children's Hospital of Eastern Ontario Pain Scale)

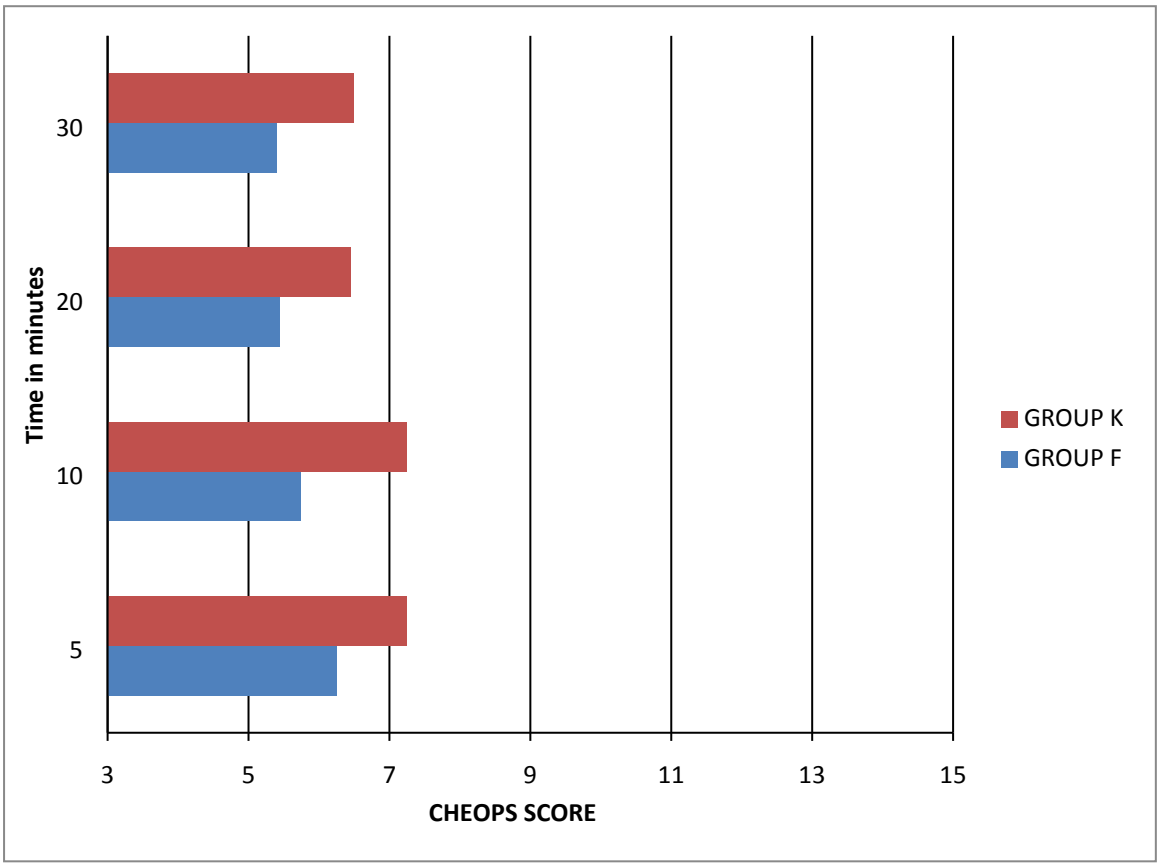
The post operative pain is assessed with CHEOPS at 5,10,15,20 and 30 minutes interval

TIME (min)	GROUP	MEAN	S.D	P VALUE
CHEO_5	F	6.25	1.97	
	K	7.25	2.12	0.131
CHEO_10	F	5.75	1.74	
	K	7.25	2.43	0.031
CHEO_20	F	5.45	0.83	
	K	6.45	2.14	0.05
CHEO_30	F	5.40	0.82	
	K	6.50	2.04	0.031

The post operative pain were compared according to the CHEOPS in two groups and found that there is higher scores in Ketamine group at 10,20 and 30 minutes. There is significant difference at 10 minutes (5.75±1.74 in Fentanyl group vs 7.25±2.43 in Ketamine group) with a p value of 0.031, at 20 minutes(5.45±0.83 in Fentanyl group vs 6.45±2.14 in Ketamine group) with a p value of 0.05 and at 30 minutes (5.40±0.82 in Fentanyl group vs 6.50±2.04 in

Ketamine group) with a p value of 0.031 with greater scores in Ketamine group which is statistically significant

CHILDREN'S HOSPITAL OF EASTERN ONTARIO PAIN SCALE(CHEOPS)



	MEAN			
TIME(min)	5	10	20	30
GROUP F	6.25	5.75	5,45	5.4
GROUP K	7.25	7.25	6.45	6.5

DISCUSSION

Several studies had been conducted comparing different agents for decreasing the incidence of emergence delirium from sevoflurane anesthesia. They also studied the pain score, time of emergence, time of extubation, time to recovery and occurrence of complications like laryngospasm, nausea, vomiting, respiratory depression, hallucination, etc with the use of those agents. Many studies had compared different doses of fentanyl and ketamine for reducing emergence delirium

In our study, Fentanyl is compared with Ketamine with regards to incidence of emergence delirium ,pain , time of emergence, time of extubation, time to recovery and occurrence of complications from sevoflurane anesthesia in pediatric patients undergoing tonsillectomy surgery. In our study, the demographic data such as age, weight, duration of surgery were comparable between both the groups.

In the study conducted by Ashraf Arafat et al[3] where 120 patients were studied for the effect of fentanyl vs ketamine on the incidence of emergence delirium from sevoflurane anesthesia in patients undergoing tonsillectomy and concluded that the incidence of Emergence delirium was significantly less in children who received either ketamine or fentanyl (15%, 17.5%) when compared to the incidence of emergence delirium in placebo group (42.5%).

But in our study we assessed the incidence of emergence delirium with ANO'S four point scale and observed that both fentanyl and ketamine were effective in decreasing the occurrence of emergence delirium. The datas obtained from both the groups were comparable at all time intervals and the values were less than 2 at all times and they are statistically not significant with a p value of > 0.05

As regard to post-operative pain assessment, in our study the pain score assessed with CHEOPS is found to be higher in ketamine group at 10,20 and 30 minutes. There is significant difference at 10 minutes (5.75±1.74 in fentanyl group vs 7.25±2.43 in ketamine group) with a p value of 0.031,at 20 minutes (5.45±0.83 vs 6.45±2.14 in ketamine group) with a p value of 0.05 and at 30 minutes (5.40±0.82 in fentanyl group vs 6.50±2.04 in ketamine group) with a p value of 0.031 which is statistically significant. But in their study there was no significant difference between the three groups at 5,10,20and 30 min post-operatively

In their study there was no significant difference between the three groups regarding recovery and discharge times . But in our study recovery time was prolonged in Ketamine group (25.15±3.39) than in fentanyl group (22.00±2.38) and the datas are statistically significant with a p value of 0.002.($p<0.05$). Similarly in contrast to their study the time of emergence (Group K 11.35±3.48 vs Group F 7.60±3.52), and the time of extubation (Group

K 14.85±4.38 vs Group F 10.75±3.32) is also prolonged in Ketamine group when compared to Fentanyl group and they are statistically significant with a p value of 0.002

In their study post-operative fentanyl consumption as rescue medication for pain and agitation was significantly more in placebo group when compared with ketamine and fentanyl group, with no significant difference between fentanyl and ketamine group.

Manal et al [25] in their study compared the effect of intravenous injection of small dose of propofol, fentanyl or ketamine at the end of surgery, just before the discontinuation of sevoflurane on the incidence and severity of sevoflurane emergence agitation in children undergoing hypospadias repair operations. In their study the incidence of emergence agitation was significantly lower in propofol and fentanyl group when compared to ketamine and control group. Consistent with this study the number of patients with emergence delirium is higher in ketamine group(8 pts out of 20 pts)when compared to fentanyl group(4 pts out of 20 pts) in our study also but the results were not statistically significant.

Ketamine was reported to have been used successfully to reduce the incidence of emergence delirium in a study conducted by Dalens et al.[12] and they reported that the IV administration of 0.25 mg/kg of ketamine or

nalbuphine 0.1mg/kg before discontinuing of sevoflurane anesthesia reduced incidence of emergence delirium in children aged 6 months to 8 years undergoing cerebral magnetic resonance imaging with no delay in awakening or discharge.

A study by Abu-Shahwan and Chowdary[1] reported that an IV injection of ketamine 0.25 mg/kg, 10 min before the end of surgery in young children pre-medicated with midazolam for dental operation reduced the incidence of emergence delirium under general anesthesia with sevoflurane without a delay in recovery.

However, conflicting results have been reported by Chen et al.[8] who demonstrated that IV administration of 0.25 mg/kg ketamine (maximum 7.5 mg) in combination with 0.5 mcg/kg of fentanyl prior to the end of sevoflurane-remifentanil based anesthesia was not effective in preventing emergence delirium in un-pre-medicated children who underwent cataract surgery compared to either 0.05 mg/kg midazolam or 1 mg/kg propofol in combination with 0.5 mcg/kg of fentanyl .

Fentanyl is a potent opioid receptor agonist, widely used and seems to be effective in preventing emergence delirium. Cravero et al.[9] have shown that addition of fentanyl 1 mcg/kg IV given 10 min before the discontinuation of inhaled sevoflurane anesthesia decreased incidence of post-operative agitation

from 56% to 12% in children scheduled for magnetic resonance imaging scans without any surgical intervention. In our study also administration of 1 mcg/kg fentanyl towards the end of sevoflurane anesthesia decreases the incidence of emergence delirium which correlates with this study.

Our study is not quite similar with previous studies because of the variations in study design; characteristics of patient population, premedication given, type of surgical procedures, the route and timing of administration of the study drugs and lastly criteria used to define and assess the phenomenon of emergence delirium by different assessment tools.

The time interval for measuring the incidence of emergence delirium, was chosen to be within 30 min during PACU stay according to results of Cole et al.,[10] who scored children every 10 min on arrival in PACU up to 1 hr and found that the peak of agitation occurs in the first 30 min after admission.

It is often difficult to distinguish between post-operative pain and emergence delirium in younger children as symptoms of both are similar so that different assessments tools have been used by different investigators to differentiate between the two. Although post-operative pain is regarded as a contributing factor in the etiology of emergence delirium there are many studies reporting the increased incidence of emergence delirium after sevoflurane, in pain-free children even if adequate analgesia given intra-operatively or even if

regional block was applied. Therefore, pain cannot be considered as the sole contributing factor to emergence delirium.

In our study pain was probably not a contributing factor in the incidence of emergence delirium, as Paracetamol suppositories was kept in all children after induction of anesthesia and the surgeon infiltrated the surgical site with 1% lignocaine.

As of complications is concerned one patient had vomiting in both the groups and one patient in ketamine group had bronchospasm. .However, no complications such as somnolence, oxygen desaturation or respiratory depression occurred during the study period and there were no episodes of hallucinations or bad dreams in the Ketamine group supporting the findings reached by Dich-Nielsen et al.[14]

Limitations of our study is that control group has not been included in our study since it was not approved in our institutional ethical committee. So the study groups could not be compared for the incidence of emergence delirium.

SUMMARY

To summarise, both Fentanyl and Ketamine are effective in decreasing the occurrence of emergence delirium.

Time of emergence, time of extubation and time to recovery is longer with Ketamine when compared to Fentanyl.

The post operative pain assessed by CHEOPS scale is higher with Ketamine at 10, 20 and 30 minutes when compared to Fentanyl.

As of complications is concerned, one patient had vomiting in both the groups and one patient in Ketamine group had brochospasm.

CONCLUSION

To conclude both Fentanyl and Ketamine are effective in decreasing the occurrence of emergence delirium. However Fentanyl has faster emergence, extubation, recovery and better pain score when compared to Ketamine.

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MASTER CHART

S.NO	GR	AGE (yrs)	WT (kg)	DURATION OF ANESTHESIA (mins)	DURATION OF SURGERY (mins)	TIME OF EMERGENCE (mins)	TIME OF EXTUBATION (mins)	TIME TO RECOVERY (min)
1.	F	9	25	60	32	7	11	20
2.	F	12	35	65	35	8	12	23
3.	F	7	20	68	40	8	10	24
4.	F	9	23	69	28	14	17	19
5.	F	9	28	79	25	20	24	26
6.	F	5	15	60	32	8	10	25
7.	F	8	17	52	25	8	9	19
8.	F	9	20	68	28	14	16	21
9.	F	9	25	59	28	9	12	23
10.	F	12	30	78	30	17	21	21
11.	F	8	20	72	34	13	15	22
12.	F	8	21	73	40	10	13	21
13.	F	12	28	78	37	14	17	25
14.	F	6	22	68	36	9	13	22
15.	F	5	11	84	35	14	25	24
16.	F	11	28	75	38	11	16	23
17.	F	12	31	60	28	10	12	19
18.	F	12	30	59	22	12	15	18

19.	F	8	20	60	28	8	14	20
20.	F	10	30	62	24	13	15	25
21.	K	8	18	51	30	4	9	22
22.	K	9	25	60	35	5	10	26
23.	K	9	20	65	40	7	8	27
24.	K	8	20	52	25	7	10	28
25.	K	12	35	59	40	3	6	25
26.	K	12	35	57	30	6	11	23
27.	K	12	35	58	35	4	9	19
28.	K	10	35	64	45	4	5	22
29.	K	10	25	59	35	5	9	23
30.	K	8	20	62	37	5	10	28
31.	K	11	25	72	45	7	10	26
32.	K	12	36	48	22	7	9	29
33.	K	12	26	55	25	9	11	27
34.	K	9	17	66	30	12	14	18
35.	K	10	30	55	25	9	11	24
36.	K	9	27	87	40	17	20	22
37.	K	5	13	59	20	13	16	30
38.	K	8	22	72	40	10	12	27
39.	K	6	22	62	30	9	13	29
40.	K	9	25	61	30	9	12	28

S.NO	GROUP	ANO'S FOUR POINT SCALE				
		5 min	10min	15min	20min	30min
1.	F	1	1	2	2	2
2.	F	1	1	2	2	2
3.	F	2	2	2	1	2
4.	F	1	1	2	2	2
5.	F	3	3	2	2	2
6.	F	1	2	2	2	2
7.	F	2	1	1	2	2
8.	F	1	2	2	2	2
9.	F	1	1	2	2	2
10.	F	1	2	2	2	2
11.	F	2	2	2	2	2
12.	F	1	1	1	2	2
13.	F	1	1	2	2	2
14.	F	3	3	2	2	2
15.	F	1	2	2	2	2
16.	F	1	1	1	2	2
17.	F	3	3	2	2	2
18.	F	3	1	1	2	2
19.	F	1	2	2	2	2
20.	F	1	1	2	2	2
21.	K	1	1	2	2	2
22.	K	1	1	2	2	2
23.	K	3	3	2	2	2
24.	K	3	3	3	2	2
25	K	1	1	1	1	2

26.	K	3	3	2	2	2
27.	K	3	1	1	1	2
28.	K	2	3	3	3	3
29.	K	1	1	2	2	2
30.	K	3	3	3	3	2
31.	K	3	3	3	2	2
32.	K	1	2	2	2	2
33.	K	1	3	2	2	2
34.	K	1	2	2	2	2
35.	K	1	3	2	2	2
36.	K	3	1	1	2	2
37.	K	1	1	1	1	2
38.	K	1	3	2	2	2
39.	K	3	2	2	2	2
40.	K	1	1	2	2	2

S.NO	GR	CHEOPS SCORE				
		5min	10min	20min	30min	complications
1.	F	6	5	4	4	Nil
2.	F	5	5	5	4	Nil
3.	F	5	5	5	6	Nil
4.	F	5	5	6	6	Nil
5.	F	12	11	7	6	Vomiting
6.	F	5	5	5	5	Nil
7.	F	5	5	7	7	Nil
8.	F	6	5	5	5	Nil
9.	F	6	5	5	5	Nil
10.	F	6	5	5	5	Nil
11.	F	5	5	5	5	Nil
12.	F	5	5	5	5	Nil
13.	F	5	5	5	5	Nil
14.	F	9	9	7	7	Nil
15.	F	6	5	5	5	Nil
16.	F	5	5	5	5	Nil
17.	F	10	9	6	6	Nil
18.	F	8	6	6	6	Nil
19.	F	6	5	5	5	Nil
20.	F	5	5	6	6	Nil
21.	K	6	5	5	5	Nil
22.	K	6	5	5	5	Nil
23.	K	11	11	7	7	Nil

24.	K	8	8	5	5	Nil
25.	K	6	6	5	5	Nil
26.	K	9	9	7	7	Nil
27.	K	10	6	6	7	Nil
28.	K	6	13	13	13	Nil
29.	K	6	5	5	5	Vomiting
30.	K	10	10	10	9	Nil
31.	K	11	11	10	10	Nil
32.	K	5	6	6	6	Nil
33.	K	5	6	6	6	Nil
34.	K	6	5	5	5	Nil
35.	K	6	9	6	6	Bronchospasm
36.	K	9	6	5	5	Nil
37.	K	5	5	5	6	Nil
38.	K	5	6	6	6	Nil
39.	K	9	7	6	6	Nil
40.	K	6	6	6	6	Nil

DEPARTMENT OF ANAESTHESIOLOGY,

KGMCH, ASARIPALLAM

EFFECT OF KETAMINE VERSUS FENTANYL ON THE INCIDENCE OF EMERGENCE AGITATION AFTER SEVOFLURANE ANESTHESIA IN PEDIATRIC PATIENTS UNDERGOING TONSILLECTOMY

PROFORMA

NAME : DATE :

AGE : SEX : WEIGHT : IP NO :

DIAGNOSIS :

PROCEDURE :

ANAESTHETIC PLAN :

ASA : I / II

DURATION OF SURGERY : DURATION OF ANESTHESIA:

STUDY GROUP (Tick appropriate)

GROUP K		**GROUP F**	

PRE-OPERATIVE VISIT

GENERAL CONDITION :

PULSE : BP : SpO2 : RR :

CVS :

RS :

TIME OF EMERGENCE : TIME OF EXTUBATION:

Table 1: POST-OPERATIVE EMERGENCE-DELIRIUM

SCORE	5 min	10 min	15 min	20 min	25 min	30 min
Score 1 (Asleep)						
Score 2 (Awake but calm)						
Score 3 (Agitated but consolable)						
Score 4 (Severe agitation)						

Table 2: POST-OPERATIVE PROFILE

S. No.	PARAMETERS	5 min	10 min	20 min	30 min
1	Cry				
2	Facial expression				
3	Verbal response				
4	Torso				
5	Touch				
6	Legs				

TIME TO RECOVERY :

Table 3: ADVERSE EFFECTS (If any)

ADVERSE EFFECT	DRUG GIVEN